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Review Article

Overview of Congenital Heart Block

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Abstract

Introduction: Autoimmune congenital heart block (CHB) is defined as a passive immune-mediated acquired medical condition that is included with the clinical manifestations collectively known as neonatal lupus. This medical condition is usually linked to placental transportation of antibodies from the mother that are usually specific for the Ro (also called SSA [Sjögren-syndrome-related antigen A]) and the La (also called SSB [Sjögren- syndrome-related antigen B]) autoantigens and involves in addition to the occurrence of cardiac abnormalities, the development of other important clinical manifestations such as cutaneous rash, liver injuries, and cytopenias in infants.

Aim of Work: This Review article will summarize the current knowledge of the clinical spectrum of autoimmune congenital heart block, by focusing on characterizing the main maternal and fetal features and the risk of the development of this autoantibody-mediated cardiac disease.

Methodology: We did a systematic search for congenital heart block using PubMed search engine and Google Scholar search engine. All relevant studies were retrieved and discussed. We only included full articles.

Conclusions: Autoimmune congenital heart block is a severe, potentially life-threatening, medical condition that is associated with the passive transfer of maternal anti-Ro and anti-La autoantibodies. However, the real incidence rate of autoimmune congenital heart block is still unknown as these antibodies are not always linked to clinical disease in the mother. Autoimmune congenital heart block is the cardiac component of a cluster of fetal and neonatal clinical manifestations that are pathogenically, epidemiologically and clinically related to these autoantibodies.

Keywords: *Congenital; Heart Block; Autoimmune; Maternal*

Introduction

Autoimmune congenital heart block (CHB) is defined as a passive immune-mediated acquired medical condition that is included with the clinical manifestations collectively known as neonatal lupus. This medical condition is usually linked to placental transportation of antibodies from the mother that are usually specific for the Ro (also called SSA [Sjögren-syndrome-related antigen A]) and the La (also called SSB [Sjögren- syndrome-related antigen B]) autoantigens and involves in addition to the occurrence of cardiac abnormalities, the

development of other important clinical manifestations such as cutaneous rash, liver injuries, and cytopenias in infants [1]. Taking into consideration the cardiac injuries, anti-Ro and anti-La antibodies cross the placenta at about week eleven of the gestation and may impact cardiac fetal development by damaging fetal conduction tissues and leading to inflammation, calcification and fibrosis, that could block signal conduction at the atrioventricular (AV) node in an otherwise anatomically-normal heart [2]. Most of autoimmune- Autoimmune congenital heart block-affected infants manifest with type three (also known as complete) atrioventricular block. These infants have a severe decline in their fetal ventricular heart rate (often fifty-to-seventy beat-per-minute; a normal range is about 120-160 beat-per-minute).

Isolated Autoimmune congenital heart block was first reported in the year 1901 by Morquio; twenty-seven years later Aylward reported the first case that was linked to a case of maternal autoimmune disease (Mikulicz disease). Studies in the 1960s and 1970s demonstrated that congenital heart block-affected mothers showed an underlying systemic lupus erythematosus (SLE), associating this congenital heart medical condition with autoimmunity. In the 1980s, the advent of fetal echocardiography and the discovery of anti-Ro antibodies in the mothers who had diseased babies paved the pathway for a more specific conception of the condition currently known as autoimmune congenital heart block. This Review article will summarize the current knowledge of the clinical spectrum of autoimmune congenital heart block, by focusing on characterizing the main maternal and fetal features and the risk of the development of this autoantibody-mediated cardiac disease [3].

Methodology

We did a systematic search for congenital heart block using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: congenital; heart block; autoimmune; maternal.

Classification and definition

Fetal congenital heart block is usually linked to two major etiologies. Anatomical heart abnormalities are found in up to forty-two percent of cases [3] and include atrioventricular septal defects, left atrial isomerism and the presence of abnormalities of the great arteries, that disturb the electrophysiological continuity between the atria and ventricles. In other cases, heart block may be a result of viral infections, drugs or myocardial ischemic and infiltrative diseases, despite that most cases of infants who have anatomically normal hearts are linked to the transference of maternal autoantibodies [1], in which case the medical condition is known as autoantibody-mediated, Ro/La-related, or autoimmune congenital heart block.

An important problem in studying autoimmune congenital heart block has been the absence of an agreed definition that is used by specialists who are involved in the treatment of affected infants and mothers, with the absence of an agreement on the main characteristics of this medical condition. In this article, we follow the definition that is used by the most experienced international groups [3], that autoimmune congenital heart block is an atrioventricular block in the infant of a mother who has autoimmune medical condition and/or positive for relevant autoantibodies, with the absence of structural abnormalities of the baby's heart that could otherwise explain the block, and which is detected in utero, at birth or within the neonatal period (up to twenty-seven days following birth).

Incidence

No previous epidemiological studies have assessed the incidence of autoimmune congenital heart block. Two previous studies, from the year 1964, concluded that the incidence rates of isolated complete congenital heart block in Finland and the USA were about 1:20,000 live births (range between 1:19,000 and 22,000). Another study that was published in the 1998 [4], calculated the mean incidence rate of isolated congenital heart block during the period between 1970 and 1994 to be about 1:17,000, with a wide annual variation of 1 in 6,500 - 64,000, and a progressive linear increase in the incidence rate. however, no data on the maternal immunological status was assessed by

these 3 studies and, thus, no specific data regarding o the incidence of autoimmune congenital heart block is present. On the other hand, studies of congenital heart block (resulting from all etiologies) detected that up to forty-two percent of cases were linked to structural abnormalities [2]; thus, assuming that the remaining fifty-six percent of cases are autoimmune, the global incidence rate of autoimmune congenital heart block is likely to be about 1 in 20,000 - 30,000.

Maternal features

Maternal autoantibodies

The present evidence that maternal anti-Ro and anti-La antibodies are essential in the pathophysiology of autoimmune congenital heart block is supported not only by several epidemiological and clinical publications, but also by multiple *in vitro* and *in vivo* experimental studies [5]. In a previously published systematic review of thirty-nine observational studies, we found that anti-Ro and/or anti-La antibodies were found in 1,230 (eighty-seven percent) out of 1,416 congenital heart block -affected mothers [6]; despite that the remaining cases were categorized as immune-negative, they largely correspond to congenital heart block that was diagnosed in children older than fifteen years or were cases where mothers were not assessed for the complete panel of congenital heart block-related autoantibodies.

Anti-Ro autoantibodies

Of the 1,416 affected mothers in the systematic review that we mentioned, 1,216 (eighty-six percent) were positive for anti-Ro antibodies, demonstrating that this autoantibody is, until now, the auto-antibody most-closely linked to autoimmune congenital heart block. Most antibodies specific for the Ro antigen detect one, or both, of the 52 kDa and 60 kDa proteins (that are encoded by different genes), and some studies have proposed that anti-Ro52 antibodies have an essential role in the development of autoimmune congenital heart block [7]. Anti-Ro52 antibodies were more common than anti-Ro60 antibodies (ninety-percent versus seventy-six percent, respectively) in mothers of autoimmune congenital heart block-affected infants; on the other hand, anti-Ro60 antibodies are more easily assessed by immunoassay if a native 60 kDa Ro protein is used as the antigen [8]. The frequency of anti-Ro60 antibodies in autoimmune-congenital heart block-affected mothers was ninety-eight percent in studies that used native antigen [5,8] and sixty-six percent in those studies that used recombinant antigen [9,10].

Given that not all mothers who are positive for anti-Ro antibodies deliver infants with congenital heart block, studies have assessed whether maternal reactivity to a specific epitope of Ro52 may confer a high predisposal to the occurrence of congenital heart block. In 2002, Salomonsson., *et al.* [11] detected a subgroup of anti-Ro52 antibodies, that is specific for amino acids 200-239 of the Ro52 protein, in all of 9 (assessed) anti-Ro52-antibody-positive mothers with congenital heart block-affected infants, showing a positive correlation with these autoantibodies (anti-p200 antibodies) and congenital heart block. On the other hand, 2 of 3 later case-control studies could not detect statistically significant variations in the prevalence of anti-p200 antibodies between affected and nonaffected mothers [12].

Most previous studies have demonstrated that mothers of infants with autoimmune congenital heart block show higher serum levels of anti-Ro and anti-La antibodies when compared to mothers with unaffected infants. About 4 out of 5 case-control studies found higher concentrations of anti-Ro52 antibodies in affected than in non-affected pregnancies [13], as did 2 of 3 studies that assessed the concentrations of anti-Ro60 antibodies [13]. Interestingly, only 1 study used native antigens for assessment, and in this study anti-Ro60 antibodies were significantly increased in mothers either with an affected infant ($P = .0002$) or with a previous history of affected infants ($P = .0001$), when compared to women with unaffected infants, while there was no significant difference in anti-Ro52 antibody titres [12].

Anti-La antibodies

Anti-La antibodies were found to be present in 672 (fifty-five percent) of 1,229 mothers of babies with congenital heart block, mostly in correlation with anti-Ro antibodies. The prevalence of these antibodies is similar to their prevalence in other patients with primary Sjögren syndrome (pSS), that is considered the systemic autoimmune medical condition with the highest proportion of anti-La-antibody-positive patients [14]. On the other hand, the presence of maternal anti-La antibodies with the absence of anti-Ro antibodies is generally

not common, and we detected (in the published literature) only fourteen cases of congenital heart block that were linked to isolated anti-La antibodies (less than one percent of reported cases of autoimmune congenital heart block) [11]. Taking into consideration the serum concentrations of anti-La antibodies, 4 out of 5 case-control studies have demonstrated higher concentrations of anti-La antibodies in affected than in nonaffected mothers, similar to studies of anti-Ro antibodies.

Other autoantibodies

The assessment of concomitant maternal autoantibodies other than anti-Ro and anti-La antibodies is usually made according to the underlying maternal autoimmune medical condition. These antibodies include anti-dsDNA and anti-Smith (Sm) antibodies in mothers with systemic lupus erythematosus, rheumatoid factor in mothers with rheumatoid arthritis, and anti-ribonucleoprotein antibodies in mothers who have mixed connective tissue disease. A specific role of these concomitant autoantibodies in the development of congenital heart block has not been assessed, despite that studies have proposed a potential independent role for anti-RNP antibodies. On the other hand, all reported cases of auto-immune congenital heart block linked to anti-RNP autoantibodies have been mothers who were also positive for anti-Ro or anti-La autoantibodies, and we detected only 1 case of a transient type one congenital heart block in an anti-RNP-antibody-positive mother who was negative both for anti-Ro and anti-La antibodies [15].

Some studies have detected other antigens (other than Ro and La proteins) linked to congenital heart block, including calreticulin, the muscarinic acetylcholine receptor M1, α-fodrin (also known as spectrin α chain, non-erythrocytic 1), α-enolase, and the serotoninergic 5-hydroxytryptamine (5-HT4) receptor [16]. Antibodies that are specific for these proteins have not been assessed in large international cohort studies, and their pathophysiological and clinical relevance is still not well-understood.

Maternal autoimmune disease

Not all mothers with congenital heart block-affected pregnancies are diagnosed (at the same time) with a specific autoimmune medical condition. A systematic review of underlying maternal autoimmune medical conditions concluded that of 856 affected mothers more than fifty-percent were categorized as asymptomatic carriers of anti-Ro and anti-La antibodies, and about fourteen percent were categorized as incomplete or undifferentiated autoimmune medical condition [17]. The other cases were mothers who were diagnosed with a specific autoimmune disease, almost all with pSS or systemic lupus dermatoses, or both; and only thirteen cases were diagnosed with other autoimmune medical conditions, including 5 with rheumatoid arthritis. More than fifty-percent of the affected mothers may have been asymptomatic, as anti-Ro and anti-La antibodies could be assessed several years before systemic lupus dermatoses or pSS are diagnosed [18]. actually, autoimmune congenital heart block can be one of the first 'indirect' manifestations of pSS in females of childbearing age [19].

Fetal features of CHB: Cardiac involvement

Atrioventricular block

Atrioventricular block is the most frequent fetal cardiac clinical manifestation of congenital heart block-affected mothers who have a positive test for anti-Ro or anti-La antibodies. Two main characteristics of auto-immune congenital heart block must be highlighted. Firstly, Atrioventricular block is diagnosed mainly during a specific time-frame. Secondly, babies with autoimmune congenital heart block are more likely than those with non-autoimmune congenital heart block to have complete Atrioventricular block, that is the most severe form.

All cases in which the time of congenital heart block diagnosis has been published have recorded the diagnosis at more than eighteen weeks of gestation [17]. On the other hand, isolated cases have been detected earlier than eighteen weeks; 1 case was at sixteen weeks, one at seventeen weeks, and 2 cases during the third month of pregnancy [20]. In more than fifty percent of the cases, Atrioventricular block was diagnosed at twenty to twenty-four weeks of gestation, and in about seventy-five percent of cases was during weeks twenty to twenty-nine weeks. Only two percent of reported cases were diagnosed at birth or within the neonatal period (less than twenty-seven

days after birth); on the other hand, whether serial echocardiographic surveillance was done from week sixteen in all cases is not known. The absence of fetal monitoring may explain a late diagnosis of autoimmune congenital heart block because anti-Ro and anti-La antibody detection is not considered a part of routine prenatal testing. With respect to the type of congenital heart block, more than eighty percent of cases that were analyzed were categorized as complete Atrioventricular block (type three), with only three percent corresponding to the less-advanced type one block.

Other electrophysiological abnormalities

Although Atrioventricular block is, until now, the main clinical manifestation of autoimmune congenital heart block, other rare electrophysiological abnormalities have been reported, including the development of transient and persistent sinus node dysfunction, long QT interval (more than 440 milliseconds), ventricular and junctional tachycardia, and atrial flutter; on the other hand, consistent correlation of these abnormalities and the presence of maternal anti-Ro and anti-La antibodies has not been detected [1].

Endocardial fibroelastosis

Endocardial fibroelastosis (EFE) is known as a form of myocardial fibrosis that could progress into the development of end-stage heart failure and even death. Prenatal echocardiographic signs of Endocardial fibroelastosis include the presence of areas of patchy echogenicity (fibrosis) on the endocardial surfaces of the fetal heart. Endocardial fibroelastosis has been reported in about seven percent of infants affected by congenital heart block (comprising nineteen percent of non- congenital heart block cardiac abnormalities), but a clear correlation with congenital heart block has not been detected [21]. The outcome of babies with Endocardial fibroelastosis was assessed by a study of more than a hundred cases in which there were fifty-three (fifty-one percent) fatalities; the mortality rate of infants with concomitant cardiomyopathy was one-hundred percent [22].

Valvular disease

Valvular diseases resulting from dysfunction of the tensor apparatus are considered to be severe complication of autoimmune congenital heart block and have been demonstrated in 1.6 percent of cases (comprising about four percent of non- congenital heart block cardiac complications). A previous study detailed the diagnostic approach and outcomes of 6 affected babies [23]. Areas of patchy echogenicity in the papillary muscle were demonstrated at weeks nineteen to twenty-two, involving mainly the tricuspid valves and the mitral valves. Severe valve insufficiencies developed prenatally or postnatally, ranging from as early as thirty-four weeks of gestation to as late as twenty-six weeks following birth; all babies required urgent valve surgery, except one who died before performing surgery.

Pregnancy outcomes

Autoimmune congenital heart block is linked to a mortality rate of nineteen percent; the majority of deaths (seventy percent) occurred in utero. Risk factors linked to death were analyzed in the US Research Registry for Neonatal Lupus [22], which included more than three hundred infants with autoimmune congenital heart block, of whom fifty-seven (seventeen percent) died. In about sixty percent of the cases, the cause of death was the development of severe cardiomyopathy. mortality rates were more than fifty percent in infants who had either Endocardial fibroelastosis or dilated cardiomyopathy and one-hundred percent in those who had both complications. Multivariate analysis demonstrated that death in utero was associated with the development of hydrops fetalis and myocarditis, and late gestational age, with a statistically significant trend for an elevated risk of death in mothers with an established diagnosis of pSS or systemic lupus erythematosus or testing positive for anti-La antibodies. In another study, Eliasson., *et al.* [24] associated mortality with the development of hydrops fetalis, impaired left ventricular function, a low ventricular rate (less than fifty beats per minute) and an earlier diagnosis of autoimmune congenital heart block (less than twenty weeks).

Conclusions

Autoimmune congenital heart block is a severe, potentially life-threatening, medical condition that is associated with the passive transfer of maternal anti-Ro and anti-La autoantibodies. However, the real incidence rate of autoimmune congenital heart block is still unknown as these antibodies are not always linked to clinical disease in the mother. Autoimmune congenital heart block is the cardiac

component of a cluster of fetal and neonatal clinical manifestations that are pathogenically, epidemiologically and clinically related to these autoantibodies. On the other hand, some studies support a different point of view, suggesting that the pathogenesis of congenital heart block involves allogenicity and that the anti-Ro and anti-La antibodies are less important biomarkers than maternal autoimmune disease per se.

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