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Original Article

Congenital heart block: current thoughts on management, morphologic spectrum, and role of intervention

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CONGENITAL HEART BLOCK IS AN UNCOMMON disorder of atrioventricular conduction affecting ~1 in 20,000 newborns, although the overall incidence may be much higher, given the high rate of foetal loss associated with congenital heart block. The hallmark of congenital heart block is atrioventricular dissociation, in which atrial impulses are not conducted to the ventricles and have no relationship with the slower ventricular rhythm. Thus, cardiac output is dependent on the intrinsic ventricular "escape" rhythm, which may be as low as 30–40 beats/minute.[1]

Congenital heart block typically appears in association with either immunological evidence of maternal connective disease or foetal structural CHD. Together, these account for ~90% of the cases; the remaining 10% are regarded as having "idiopathic" congenital complete heart block.[2]

The understanding that congenital heart block in the absence of structural heart disease is strongly linked to mothers with connective tissue disease was established 30 years ago.

Neonatal lupus syndrome is a model of passively acquired autoimmunity in which the pregnant woman's serum contains specific antibodies to 52- or 60-kDa SSA/Ro, and/or 48-kDa SSB/La, which cross the placenta and are associated with the development of congenital heart block in the foetus, and/or a transient rash or various liver and blood cell abnormalities in the newborn. All the manifestations of neonatal lupus disappear with the clearance of maternal antibodies from the foetal circulation, except congenital heart block, which is irreversible.[3]

The relative rarity of autoimmune-associated congenital heart block has posed a challenge to clinical and epidemiologic researchers. In 1994, the establishment of the National Neonatal Lupus Registry had enabled the acquisition of larger and more statistically reliable series.[4]

Maternal autoantibodies, 48-kDa SSB/La, 52-kDa SSA/Ro, and/or 60-kDa SS/Ro rib nucleoproteins, account for at least 90% of cases with isolated congenital heart block. These autoantibodies are prevalent in 2% of all pregnant women. Having these autoantibodies carries a risk of 1–2% of major foetal cardiovascular pathology. Therefore, whereas the incidence of congenital heart block is much larger in foetuses of antibody-positive mothers, the individual risk for a mother with such antibodies is generally quite low. Only 10% of the mothers have been diagnosed with connective tissue disease at the time of foetal congenital heart block diagnosis. Congenital heart block typically develops between 18 and 24 gestational weeks. The recurrence rate is 16–18%.[3–5]

Protocol of management

Firm guidelines for the management of the foetus identified with congenital heart block and the foetus with a normal heartbeat but a high risk of developing congenital heart block are not established. Current management postulates that there is an orderly disturbance in the foetal conduction system in which initial inflammation precedes subsequent scarring. The discovery of first- or second-degree atrioventricular block appears to represent a window of opportunity with regard to prevention of permanent complete atrioventricular block.

The aim of management is to avoid congenital heart block by early identification and treatment of conduction anomalies. On the basis of the proposed pathogenesis of congenital heart block, treatment approaches focus on reduction of a generalised inflammatory response and prevention of fibrosis. The mainstay of treatment is steroids.[3,5,6]

Given the identification of advanced block and severe cardiomyopathy within 1 week of a normal echocardiogram and its usual occurrence before 24 weeks of gestation, it would be appropriate to perform weekly echocardiograms between 16 and 26 weeks of gestation, and biweekly echocardiograms between 26 and 32 weeks, with close evaluation of

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P-R interval. The decision to begin treatment with dexamethasone in the mother is based on signs of first- or second-degree heart block, or the presence of biomarkers of inflammation. Treatment with β-mimetics is reserved for cases with heart rate <55 beats/minute or signs of hydrops or ventricular dysfunction. Prophylactic therapy is an attractive option under investigation.

Electrocardiogram should be performed on all neonates, and any conduction abnormality at birth should be followed by a cardiologist; however, no later conduction abnormalities have been reported to date in an infant with normal sinus rhythm at birth.

There are several controversial points in the understanding and management of autoimmune-mediated congenital heart block. First, the pathogenetic mechanism is not completely understood, and thus it is difficult to establish a strategy to prevent it. Second, the most extended tool to evaluate rhythm in the foetus is Doppler echocardiography, but the limits of normality are not clearly defined. Third, treatment with steroids is extended, but the safety and efficacy have not been established.

Pathogenesis

It is now generally accepted that the pathogenesis of autoimmune congenital heart block involves the transplacental passage of maternal anti-SSA/Ro and SSB/La antibodies.[7] The known consequence is atrioventricular block. However, there are several questions without a complete answer. The maternal antibody is necessary but not sufficient to cause disease. This suggests the contribution of foetal and environmental factors. Thus, the pathologic cascade to scarring is rapid but variable. Only in 2% is the cascade fully executed with advanced block. If we can understand why the other 98% avoid damage strategies, treatment could be developed.[5,8,9] If at least one accepts that the maternal antibody is responsible for initiating injury, then understating the mechanism by which this occurs is important.

To explain the casual relationship of anti-SSA/Ro anti-SSB/La antibodies with the development of congenital heart block, three basic requirements should be satisfied. First, the candidate antigens must be present in the target foetal tissues; second, the cognate maternal autoantibodies must be present in the foetal circulation; and third, these antigens must be accessible to the maternal antibodies. The antigens are intracellular in healthy cardiocytes. Moreover, the IgG cannot cross the sarcolemma. There are two main possibilities under investigation. A mechanism to translocate these antigens to the cell surface supports the theory of apoptosis. A cross-reaction with other antigens present in the cell surface supports the C-channel hypothesis.[10]

During embryologic stages, non-inflammatory removal of apoptotic cells occurs without disturbing the overall integrity of the developing tissue.[11] Immunohistologic evaluation of the hearts from the foetuses dying with congenital heart block has revealed exaggerated apoptosis.[12]

This physiological process may be altered if these antigens translocated to the cell surface enter in contact with the maternal anti-Ro/La antibodies, which may inadvertently divert normal clearance of apoptotic cardiocytes by healthy cardiac myocites towards clearance by professional macrophages with the release of inflammatory and fibrosing cytokines.[13]

The formulation of the calcium channel hypothesis is driven by the fact that atrioventricular node electrogenesis and action potential propagation to the ventricle are under the control of L-type calcium channel. L-type calcium channel is a protein complex that consists of an α1 pore-forming subunit, and other accessory subunits.[14,15]

The calcium channel hypothesis explains congenital heart block as an acquired channelopathy, proposing that circulating maternal antibodies directly bind to specific epitopes of the calcium channel pore-forming subunit and inhibit calcium entry to the cell.[8,14] This inhibition of the calcium channel function by anti-Ro/La antibodies is, per se, sufficient to cause electrocardiographic abnormalities similar to those seen in congenital heart block. Inhibition of these channels may exert negative inotropic effect and/or electro-mechanical uncoupling leading to contractile dysfunction. This could explain electrocardiographic anomalies and cardiomyopathy.

None of these theories explain the pathogenesis of congenital heart block completely and more importantly why some foetuses avoid permanent damage, suggesting that additional factors are required to promote disease manifestation. Deeper knowledge of the cellular-level process will give us the management clues in the future.

Treatment

Nowadays, it is accepted that treatment with dexamethasone is not indicated for prophylaxis, even in anti-SSA/Ro-positive women and mothers of infants with neonatal lupus. There is evidence of non-improved mortality or morbidity in cases of established third-degree atrioventricular block. If too early is not indicated, and too late is not effective, then the critical time or the "window of opportunity" to treat is when the P-R interval is prolonged; however, atrial signals continue to reach the ventricles – first- or second-degree block – or when signs of myocardial dysfunction alone are present.[1,3,5]

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Investigators over the past several years have attempted to predict which foetus will be at risk for advanced conduction abnormalities by identifying a biomarker for less severe or incomplete disease, in this case, P-R interval prolongation or first-degree atrioventricular block. The most extended technique is Doppler echocardiography, but the sensibility and specificity for first-degree atrioventricular block are very variable in the different reports. Existing data regarding the true incidence of first-degree atrioventricular block and its potential to predict later progression to more advanced block are conflicting.[3,8]

Identification of prolonged P-R

Friedman et al. published their results of the P-R Interval and Dexamethasone Evaluation study, in which serial Doppler echocardiography studies on high-risk pregnancies were conducted. Of the 127 pregnant women with anti-SSA/Ro antibodies enrolled in the study, 95 women completed an evaluable course in 98 pregnancies. The protocol included weekly foetal echocardiograms in gestational weeks 16–26, and biweekly studies in weeks 26–34. P-R intervals of 150 milliseconds or more were considered prolonged, consistent with first-degree block. Of the foetuses, three had third-degree block; none had a preceding abnormal P-R interval. Tricuspid regurgitation preceded third-degree block in one foetus, and an atrial echo density preceded block in another foetus. Another two foetuses had P-R intervals >150 milliseconds. Both were detected at or before 22 weeks, and each reversed within 1 week with 4 mg dexamethasone. The electrocardiogram of one additional newborn revealed a prolonged P-R interval persistent at 3 years, despite normal intervals throughout gestation. No first-degree block developed after a normal electrocardiogram at birth. Heart block occurred in 3 of 16 pregnancies (19%) in mothers with a previous child with congenital heart block, and in 3 of 74 pregnancies (4%) in mothers without a previous child with congenital heart block or rash. Thus, the authors concluded that prolongation of the P-R interval was uncommon and did not precede more advanced block, based on their use of Doppler echo detection. Interestingly, the authors reported that advanced block and cardiomyopathy can occur within 1 week of abnormal echocardiograms without prior first-degree block. They also pointed out that echo densities and moderate/severe tricuspid regurgitation merit attention as early signs of injury.[16]

Previously, Sonesson et al. reported a high incidence of first-degree atrioventricular block in a prospective study. Of the total number of Ro 52-seropositive women, 24 were followed up weekly between 18 and 24 weeks of gestation, with two Doppler echocardiographic methods designed to estimate the time delay between hemodynamic events caused by atrial and ventricular depolarisation. A total of 284 women with normal pregnancies served as controls. A P-R interval >135 milliseconds was considered abnormal. Of the 24 foetuses in the Ro 52-seropositive women, eight had signs of first-degree atrioventricular block, one of which progressed to complete atrioventricular block, and six spontaneously reverted to normal conduction before or shortly after birth. The authors concluded that Ro 52-seropositive pregnant women frequently carry foetus with first-degree atrioventricular block, and progression to a more severe degree of block may occur in some.[17]

These contradictory results using the same Doppler echo technique can be explained from the technical definition of abnormal P-R interval as 135 milliseconds in the Sonesson study in comparison with the 150 milliseconds threshold used by the P-R Interval and Dexamethasone Evaluation study. Interestingly, in the P-R Interval and Dexamethasone Evaluation study, all foetuses with P-R intervals of 135–150 milliseconds spontaneously reversed by the next echocardiogram. This highlights the need to establish a universal cut-off for abnormal P-R interval to control the same population and compare the different protocols of treatment.

Rein et al published a study in Circulation in March 2009 using tissue velocity imaging for the detection of first-degree atrioventricular block. They performed serial spectral tissue Doppler foetal kineto cardiogrammes (FKCG) to track first-degree atrioventricular block in anti-SSA/Ro 52 kDa and 60 kDa, and anti-SSB/La-positive women. The initial FKCG was performed weekly from gestational weeks 13–14 to week 26, and then twice a month until delivery. Of the 70 foetuses, 6 (8.5%) were diagnosed with prolonged P-R (first-degree atrioventricular block) compared with normal controls at comparable gestational ages. When a foetus was diagnosed with first-degree atrioventricular block, the mother was treated with fluorinated steroids. All six foetuses diagnosed with first-degree atrioventricular block showed improvement of atrioventricular conduction following 1 week of fluorinated steroid treatment, and none of them progressed to congenital heart block. These findings suggest that FKCG can detect first-degree atrioventricular block in the foetus exposed to maternal anti-SSA/Ro or SSB/La antibodies, or both in about 8.5% of pregnancies. Fluorinated steroids administered upon detection were associated with a return to normalised atrioventricular conduction in foetuses with first-degree atrioventricular block.[18] More studies are necessary to demostrate the accuracy of

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tissue Doppler velocity imaging for the detection of first-degree atrioventricular block.

In this line to look for the best tool to diagnose first-degree atrioventricular block, a comparison was made between mechanical P-R and electrical P-R intervals obtained prospectively using Doppler and non-invasive foetal electrocardiogram in 52 Ro/La pregnancies in 46 women. The authors concluded that electrical P-R is better than mechanical P-R at differentiating between normal and prolonged P-R intervals, suggesting that foetal electrocardiogram is the diagnostic tool of choice to investigate the natural history and therapy of conduction abnormalities in Ro/La pregnancies.[19]

Definitions of first-degree atrioventricular block vary, but the techniques themselves are valid and reliable. Accurate identification of the foetus in whom first-degree block unambiguously represents a warning sign would be a major advance, as early disease may be reversible.

To treat or not to treat a mother when a first-degree atrioventricular block is identified

The concern is whether some, and, perhaps, even majority, of the foetuses with first-degree atrioventricular block would reverse spontaneously, and therefore whether we could avoid unnecessary foetal and maternal exposure to steroids, with associated morbidity to both the mother and the foetus. In addition to the known adverse effects of steroids in adults and in pregnancy, foetal adverse effects may include intrauterine growth restriction, oligohydramnios, adrenal suppression, learning disabilities, and decreased brain growth, as well as late hypertension and possible diabetes.[20]

Prolongation of the foetal mechanical P-R interval has not convincingly proved utility in predicting advanced heart block in a prospective study controlled by serial echocardiography on 165 foetuses of 142 anti-Ro/La antibody-positive women. Their protocol included weekly evaluation of foetal atrioventricular conduction between 19 ranging from 17 to 23 and 24 ranging from 23 to 35 gestational weeks. Atrioventricular times were compared with institutional reference data and with postnatal electrocardiograms. Of the 150 foetuses with persistently normal atrioventricular conduction throughout the observation period, a diagnosis of congenital atrioventricular block was subsequently made in one foetus at 28 weeks, after the serial evaluation had ended. Of the 15 untreated foetuses, either with atrioventricular prolongation between 2 and 6 z-scores, or with type 1 second-degree block, progressive heart block developed in none of them. Of these 15 foetuses, 3 (20%) had a neonatal diagnosis of first-degree block that spontaneously resolved or had not progressed on follow-up examinations. No other cardiac complications were detected. Thus, they proposed that transplacental treatment should be restricted to those foetuses with progressive atrioventricular block, or with additional findings of autoantibody-mediated pathology, such as endocardial fibroelastosis and effusions. Moreover, in isolated atrioventricular prolongation up to 6 z-scores, close monitoring for disease progression without treatment is recommended.[21]

Although dexamethasone maternal therapy has become popular, outcome data are limited with regard to its safety and efficacy. Safety concerns are amplified because pregnancy is the only situation with the potential of a 200% mortality rate (mother and child). Data from a prospective open-label multicentre study, carried out as part of the P-R Interval and Dexamethasone Evaluation study, analysed dexamethasone treatment in congenital heart bock.[22] Specifically, the study comprised 30 pregnancies treated with dexamethasone – 22 cases third degree, 6 cases second degree, and 2 cases first degree – and 10 untreated pregnancies – 9 cases third degree and 1 case first degree. The initial median ventricular rates, age at diagnosis, and degree of cardiac dysfunction were similar between groups. In all, six deaths occurred in the dexamethasone group. There was no reversal of the third-degree block, with therapy or spontaneously. In the six foetuses treated with dexamethasone, one out of six with second-degree block progressed to third-degree block, and three remained in second-degree, one paced and two progressing to third-degree block; two reverted to normal sinus rhythm, with one progressing to second degree. Dexamethasone reversed both foetuses with first-degree block to normal sinus rhythm in 7 days, with no regression upon discontinuation. Absent dexamethasone, the only first degree detected at 38 weeks had normal sinus rhythm at birth – overall stability or improvement four out of eight dexamethasone versus one out of one non-dexamethasone. Median gestational birth age was 37 versus 38 weeks, dexamethasone versus non-dexamethasone ($p = 0.019$). Prematurity and small gestational age were restricted to the dexamethasone group. Pacemaker use and growth parameters at birth and 1 year were similar between groups.

They concluded, as is known, that third-degree block is irreversible. However, the most important consequence of this study is that the progression of second- to third-degree block is independent of dexamethasone treatment. Thus, they propose that treatment of first- or second-degree block should be weighed against potential steroid side effects such as growth restriction.

Owing to difficulty in determining the appropriate cut-off for first-degree block and the

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contradictory data on the progression to more advanced block, the decision to treat is usually based on personal experience or local protocols.

Endocardial fibroelastosis and cardiomyopathy

Evidence is emerging that, in addition to conduction disease, 10–15% of the affected offspring will have a life-threatening cardiomyopathy. This injury can occur in utero or postnatally, even as late as 9 years of life.[23] The prognosis reported for foetuses and infants with diffused cardiomyopathy/endocardial fibroelastosis is generally poor, with death or need for cardiac transplantation in 85% of the cases, despite the pacemaker therapy.[24] The finding of endocardial fibroelastosis in the absence of atrioventricular block and the evolution of late cardiomyopathy/endocardial fibroelastosis, despite adequate pacing, suggested that cardiomyopathy/endocardial fibroelastosis and atrioventricular block may be two separate disease manifestations in neonatal lupus syndrome, but a casual relationship cannot be ruled out.[25] Some reports suggest that treatment with steroids in foetus with signs of myocardial inflammation could improve the outcome of the disease.

In 2011, a retrospective, multicentre study on 20 consecutive cases of cardiomyopathy/endocardial fibroelastosis autoimmune-mediated disease managed with a treatment protocol with steroids and intravenous immunoglobulin between 1998 and 2009 was published.[26] Of the 20 foetuses, 16 received dexamethasone, and 9 received β-sympathomimetic therapy. Intravenous immunoglobulin was administered prenatally to 9 (47%) foetuses. Of the 19 live births, 14 were pre-term. At birth, nine foetuses had reduced or borderline ventricular systolic function. Of the total number of neonates, 12 (63%) underwent permanent pacemaker therapy, 11 were administered intravenous immunoglobulin in the first few days, and 15 were administered steroids. A total of 16 (80%) patients were alive at the moment of the report, and none had required cardiac transplantation. They concluded that using intravenous immunoglobulin and steroids to treat autoimmune-associated cardiomyopathy may significantly improve the outcome in these patients, with a particularly bad prognosis.

Prophylactic treatment

The development of a new prophylactic therapy is attractive. A therapy other than dexamethasone, to be administered early in pregnancy before the onset of the disease, perhaps targeted at the highest risk pregnancies such as in women with prior affected offspring. Intravenous immunoglobulin is a promising agent, which might have an effect at several levels of the proposed pathologic cascade.

On the basis of Simon's two-stage optimal design studies, two multicentre, prospective, open-label studies have been reported, with the same protocol of treatment.[27,28] They enrolled 35 mothers with a prior affected pregnancy who received prophylactic intravenous immunoglobulin to prevent recurrence. Combining data generated from the two studies, in which the prior pregnancy was congenital heart block and not rash, there were six cases of recurrent congenital heart block in 33 mothers (15 European and 18 PITCH), which is consistent with the recently reported recurrence rate of 17.4%, and confirms that intravenous immunoglobulin at a dosage of 400 mg/kg administered every 3 weeks beginning at week 12 of gestation is not effective in reducing the incidence of recurrent disease. Another treatment protocol, earlier administration or higher dosage, may improve treatment outcomes in the future.

Conclusions

Congenital heart block is irreversible. The possibility to detect early signs when damage is reversible with treatment supports the necessity of close monitoring of anti-SSA/Ro, SSB/La mothers. Deeper knowledge of the ethiopathology of autoimmune-mediated congenital heart block will give us the clues to improve our clinical management. In the next few years, we are going to see an improvement in our understanding of the pathogenesis that may lead us to new options of treatment, such as TGF-β inhibition or calcium agonists.

P-R prolongation is the most extended way to evaluate early damage; however, accurate identification of the foetus in whom first-degree block unambiguously represents a warning sign would be a major advance as early disease may be reversible.

If the biomarkers of inflammation – P-R prolongation, tricuspid regurgitation, or unexplained echo density – are identified, the consideration of benefit from steroids to prevent a lifelong condition must be weighed against potential toxicity of this treatment and the fact that it has not proved to be effective.

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