REVIEW ARTICLE

Neonatal Congenital Heart Block

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Congenital Heart Block (CHB) is the most serious complication of neonatal lupus erythematosus. Transplasental transfer of maternal anti-SSA/Ro or anti-SSB/La antibodies around 12th week of gestation is associated with development of CHB. This may lead to inflammation, fibrosis and scarring of fetal conduction system in the early second trimester. Different degrees of atrioventricular (AV) block may be seen in the affected fetus. First and second-degree AV blocks may change in severity; however, third degree AV block is irreversible. CHB is mostly diagnosed between 18- 24th weeks of gestation. Even if most of the mothers carrying autoantibodies of several rheumatic diseases such as systemic lupus erythematosus or Sjogren's syndrome are not aware of their diseases until their children are born with CHB, it is recommended that antibody-positive mothers or the mothers having babies with neonatal lupus erythematosus should be referred for close fetal echocardiographic surveillance beginning from the early second trimester. Although their utility is still controversial, various therapeutic regimes such as sympathomimetic, plasmapheresis, steroids, intravenous immunoglobulin, digoxin, diuretic and *in utero* pacing have been used for intrauterine treatment of CHB. Aggressive medical treatment is coupled with pacing in infants who do not respond to medical therapy alone.

Key words: *Congenital heart block, Neonatal lupus.*

Neonatal lupus erythematosus (NLE) is considered as a model of passively acquired autoimmune disease characterized by the transplacental passage of anti-SSA/Ro and anti-SSB/La antibodies from affected mother to fetus. Characteristic clinical features of NLE are transient rash, congenital heart block (CHB), hepatobiliary dysfunction, and hematological, neurological and pulmonary abnormalities. Cutaneous NLE is present in 15–25% of affected children. The dermatitis tends to resemble the rash of subacute cutaneous lupus erythematosus or annular erythema all around the body and not the malar rash of systemic lupus erythematosus. Liver involvement in NLE is usually asymptomatic or it may present with elevated liver function tests, which may be the evidence of cholestasis. Although hematological involvement is mostly asymptomatic, neutropenia, thrombocytopenia and anemia are the most common hematologic abnormalities seen in affected offsprings. The most serious, life-threatening and irreversible complication of NLE is CHB, mostly diagnosed between 18-24th weeks of gestation [1-5]. Unlike CHB, the noncardiac symptoms of NLE usually resolve within a few months after birth, coincident with the clearance of the maternal antibodies from the child's circulation.

If the mother is anti-SSA/Ro positive, the risk of CHB in the fetus is about 1-2%. Presence of anti-SSB/La antibodies in addition to anti SSA/Ro increases this risk to 5% [6, 7]. The risk of recurrence of CHB is 5-17% for the second child and rises up to 50% for the subsequent births [7-9]. Nearly half of the mothers carrying autoantibodies of SLE are not aware of their disease until their children are born with CHB. These mothers are asymptomatic at delivery and are identified only by the birth of an affected child [6, 10]. The identification of isolated CHB in a fetus, particularly in the late second trimester, predicts with only 85% certainty that the mother will have autoantibodies against the intracellular SSA/Ro–SSB/La ribonucleoproteins [11]. Therefore, incidental detection of fetal bradicardia in the antenatal ultrasound should warrant us for further screening of maternal anti-SSA/Ro and anti-SSB/La antibodies.

Maternal health status, use of steroids during pregnancy, antibody status, severity of disease in the first affected child and the sex of second child are not predictors of outcome of subsequent pregnancies [12]. However, some authors suggest that due to the increased risk of cardiac NLE, the mothers who have babies with cutaneous lupus should be monitored closely during subsequent pregnancies [13].

PATHOGENESIS

Tissue injury in the fetus is presumed to be dependent on the $Fc_{\tilde{a}}R$- mediated transplacental passage of maternal

IgG autoantibodies. Anti-SSA/Ro and anti-SSB/La antibodies bind to fetal cardiocytes and inhibit the normal physiologic removal of apoptotic cells, thus resulting in inflammatory reaction and fibrosis of the cardiac conduction system. Other possible mechanisms are cross-reactivity of SSA/SSB antibodies and down-regulation of L-type Calcium channels or their inhibition by autoantibodies. Furthermore, some investigators have studied the electrophysiologic and molecular mechanisms of congenital heart block and concluded that anti-SSA/Ro antibodies might have direct arrhythmogenic activity (14,19). Finally these processes cause myocarditis, hemorrhage, fibrosis, calcification and necrosis in conduction system, which result in development of a variable degree of heart block, myocardial dysfunction, and/or endocardial fibroelastosis (EFE).

Although absolute antibody titers have not been previously linked to the risk of cardiac involvement, a recent single center investigation by Jaeggi, *et al.* [20] showed that this risk was 85% when a fetus was exposed to anti-Ro antibody levels >100 U/mL. In the same study, it was seen that cardiac involvement was not present in pregnancies with anti-Ro levels <50 U/mL. On the other hand fetal and neonatal cardiac manifestations were found to be independent from anti-La antibody titers [20]. In contrast to this study, Gordon, *et al.* [21] found that the children of anti-Ro positive mothers had 2% risk of having AVB, which increased to 3.1% if the mother was anti-La positive as well. Although these antibodies appear to be necessary, they are not sufficient to explain the development of cardiac NLE because the majority of women with anti-Ro and La (positive and/or high) have normal pregnancy outcome. As the cardiac involvement is the most serious complication of NLE, routine screening of anti-SSA/Ro and anti-SSB/La antibodies in the mothers with autoimmune disorders such as SLE, Sjogren's syndrome should be performed in the antenatal period for early detection and successful management.

Although maternal autoantibodies are considered to be responsible for CHB in NLE, some authors have found that these antibodies are directly involved in the pathogenesis of CHB but are not the only cause. They have shown that cardiac involvement may occur only in one of the twins or two of the triplets exposed to maternal SSA/Ro and SSB/La autoantibodies [22,23]. Environmental factors or several intrauterine, fetal or maternal factors and genetic predisposition may affect the pathogenesis of CHB in neonatal lupus.

CHARACTERISTICS

CHB is usually permanent and the clinical manifestations depend on the ventricular rate. Depending on the degree of scarring, the severity of conduction disorder may change: most affected fetuses retain their normal sinus rhythm, whereas some others show subclinical first-degree block or advanced block. CHB is an injury unique to some phases of development, because it has never been reported in the maternal heart despite the presence of identical antibodies in the maternal circulation. Even though the congenital heart block is irreversible, there are a few isolated cases in which AV nodal rhythm turns to sinus rhythm spontaneously. Only in one case it was reported that the AV node responded to exercise with accelerated heart rate although the patient had CHB [24, 25]. Low heart rate may result in fetal hydrops or neonatal heart failure. Some newborns can compensate with low heart rate, although most of them need pacemaker implantation [27, 28].

The authors have shown that 15–20% of affected fetuses develop more diffuse myocardial disease before birth and others may have myocardial dysfunction after birth even with adequate pacemaker therapy. Isolated EFE and cardiomyopathy may be seen in NLE without conduction abnormalities. In some babies born to mothers with lupus autoantibodies, EFE is diagnosed prenatally, whereas in others it is diagnosed several years after birth. Development of late onset cardiomyopathy or EFE may be due to the progression of the perinatal impairment of myocardium, which requires a secondary trigger such as viral infection or genetic predisposition, or may be induced by pacing or metabolic disorders [29-32].

TREATMENT

Various therapeutic regimes have been used for intrauterine treatment of CHB including; sympathomimetics, plasmapheresis, steroids, intravenous immunoglobulin, digoxin, diuretic and *in utero* pacing. The usefulness of these treatments still remains controversial.

Fetal management

Corticosteroid

Macrophage infiltration was demonstrated in autopsy studies of the fetuses dying of CHB, and *in vitro* studies showed the release of TNFα from macrophages when co-cultured with anti-SSA/Ro, anti-SSB/La antibodies bound to apoptotic human fetal cardiocytes [14,33]. Therefore, corticosteroid treatment may be useful; but only fluorinated corticosteroids are not metabolized by placenta and remain active in fetal circulation when given to the mother. Routine prophylactic treatment is not recommended. In the study of Jaeggi, *et al.* [34] one year survival was found to be 90% in the dexamethasone treated group, whereas 46% in the untreated group [34]. Friedman, *et al*. [35] compared 30 pregnant women who

had received dexamethasone treatment with 10 pregnant women who had not received medication and found that 3rd degree block was irreversible and 2nd degree block progressed to 3rd degree despite dexamethasone treatment. A potential benefit of dexamethasone in reversing 1st or 2nd degree block was supported in rare cases [35]. A review of 19 studies in which 93 cases of fetal heart block were treated with maternal steroid therapy showed that complete CHB persisted in 59 cases despite adequate maternal dexamethasone or betamethasone treatment. On the other hand, among 13 fetuses with incomplete heart block, 3 had reduction in degree of heart block and one reverted to sinus rhythm after maternal steroid therapy [36]. Maternal steroid treatment did not decrease the incidence of heart block in nine studies (43 cases) [36]. Numerous side effects of maternal steroid administration were revealed in these studies [36]. Therefore, it is recommended that steroid use should be limited to <10 weeks to avoid maternal and fetal adverse effects, such as fetal growth restriction and oligohydramnios [37].

Intravenous Immunoglobulin

IVIG might show its effect by several possible mechanisms including autoantibody neutralization by anti-idiotype antibodies, accelerated clearance of pathogenic autoantibodies via competitive inhibition of the neonatal immunoglobulin Fc receptors, complement neutralization with consequent reduction of inflammatory response and fibrosis. Kaaja, *et al*. [38] conducted a study with 8 high-risk pregnant women (anti-SSA/Ro or anti-SSB/La positive; previous delivery with CHB) and treated them with IVIG to prevent the development of CHB in their fetuses. All patients were treated with 1g/kg of IVIG at 14th and 18th weeks of gestation and seven patients received concomitant treatment with high dose oral prednisolone. One patient gave birth to a child with CHB. Anti-SSA/Ro titers were reduced in 6 patients [38]. In another study, 24 pregnant women, 15 of whom received IVIG infusion and remaining as control group, were included [39]. IVIG was administered at a dose of 400 mg/kg at 12th, 15th, 18th, 21st and 24th weeks of gestation. CHB developed in 20% in the treatment group and in 11% in the control group. This IVIG was non-effective at 400 mg/kg dose with these dose intervals for prophylactic therapy of CHB in high-risk mothers [39]. In another study, 20 anti-SSA/Ro positive mothers, with previous children with CHB/neonatal lupus rash, were given 400 mg/kg IVIG at every 3 weeks from 12th to 24th weeks of gestation. Only 3 fetuses had CHB at 19th, 20th, and 24th weeks of gestation. No significant changes were detected in maternal titers of anti-SSA/Ro, SSB/La antibodies over the course of therapy [40].

β-sympathomimetic Treatment

Several studies have found that a ventricular heart rate <55 beats per minute is a risk factor for fetal and neonatal death and have recommended transplacental treatment with α-sympathomimetic to increase the heart rate [41, 42]. Miyoshi, *et al*. [37] showed that fetal ventricular heart rate did not influence the development of fetal hydrops and prognosis, but treatment with a α-sympathomimetic agent was significantly associated with improved bradycardia [37]. However, in the study of Maeno, *et al*. [43], it was shown that fetal ventricular heart rate increased by more than 10% in five of eight fetuses and fetal hydrops resolved in one after administration of α- sympathomimetic [43]. Hutter, *et al*. [44] obtained an improved survival rate of >90% by initiating maternal high dose dexamethasone at the time of CAVB detection and maintaining this dose during pregnancy with addition of α-sympathomimetic to keep the fetal heart rate above 55 beats/min [44]. In case of persistent fetal bradycardia <55 beats per minute, dexamethasone administered to mothers at the time of diagnosis of fetal heart block in combination with α-sympathomimetic therapy significantly improved survival compared with untreated fetuses [34]. There are also reports of unsuccessful attempts at direct fetal pacing [45].

Neonatal and infant management

Newborns with AV block should be taken into the intensive care unit for central line placement, optimization of acid/base status, inotropic drug infusions and mechanical ventilation, if necessary; soon after birth if they have impaired cardiac functions and low cardiac output. Planned early pacing of high-risk neonates with CHB potentially reduces the adverse consequences of profound bradycardia and asystole soon after birth in the milieu of increasing metabolic demands. Prematurity, low birthweight, poor hemodynamic status and metabolic acidosis are the factors affecting the performance and success of pacing. In a study by Glatz, *et al.* [46] early diagnosis, use of maternal steroids, close follow-up and early placement of temporary epicardial pacing leads after planned deliveries for the severely affected newborns with isolated CHB were recommended. The use of temporary epicardial ventricular pacing wires implanted by a minimally invasive approach can be used successfully as a bridge to a permanent pacemaker. Permanent pacemakers were implanted when patients reached a point of clinical stability and achieved a weight deemed suitable for a permanent pacing system (typically >2 kg) [46]. On the other hand, Kelle, *et al*. [47] demonstrated that implantation of dual-chamber

epicardial pacemakers to the neonates with CHB was technically feasible and yielded a stable, long-term pacing system with an excellent outcome [47].

In the study of Buyon, *et al*. [6] 67 of 107 (63%) newborns and infants whose mother had positive anti-SSA or anti-SSB antibodies needed pacemaker implantation. Of those who needed pacemaker therapy, 35 underwent pacemaker implantation within the first 9 days of life, 15 within one year, and 17 after one year [6]. In another study, permanent pacemaker therapy was applied to 67 of 102 cases with CHB. The ratios of intervention, related complications and need for reintervention were higher in cases diagnosed in prenatal period then those diagnosed in postnatal period [29].

PROGNOSIS

CHB carries a significant risk of morbidity and mortality (15-30%), especially *in utero* or in the first few months of life. 63% of all recognized cases are reported to require pacemaker implantation before reaching adulthood. In another study, out of 65% of cases who required lifelong pacing, 20% resulted in mortality [6,7,48]. In several studies, it has been demonstrated that mortality due to CHB mostly occurs in fetal, neonatal or infant periods. In the study of Buyon, *et al.*, [6] including 113 patients with CHB, the neonatal and fetal mortality rate was found to be 19%. Eronen, *et al*. [49], reported that the mortality was 16% among 91 infants with CHB, with deaths mostly occurring in infancy. In another study of 36 fetuses with CHB and structurally normal heart, the mortality occurred in 9%, occurring in utero or neonatal period [27]. In the study of Jaeggi, *et al.* [34], 45% of CHB cases diagnosed in utero died. In the presence of hydrops, reported mortality rates for infants born with CHB exceeded 80% [27, 29].

Identified factors for poor prognosis include: hydrops fetalis, low heart rate (<50- 55 beats per minute) or sudden rapid drop in heart rate, endocardial fibroelastosis (EFE), dilated cardiomyopathy, valvular dysfunction, low birth weight, male sex, delivery at <34 weeks of gestation, and complications from prematurity or neonatal lupus. The significant echocardiographic predictors of mortality are only hydrops and EFE [6, 27, 29, 49, 50].

Separate analyses on fetuses dying *in utero* and children dying after birth revealed similar echocardiographic predictors of mortality. In the analyses limited to *in utero* deaths, it was found that the stage of gestational age at which cardiac NLE had taken place might help the prediction of outcome. This finding suggests that earlier injury results in more extensive damage to the cardiac structures. If an earlier event targets a major part of the fetal heart, it may result in a more severe lesion, such as cardiomyopathy. In a later event in which the exposed and vulnerable targets are restricted to the isolated conduction system tissues, the insult may not be lethal [51].

There are only a few studies about the long-term survival of the patients with autoimmune-mediated CHB. In the study of Moak, *et al*. [33], 16 infants with CHB (12 diagnosed *in utero*) developed late onset LV cardiomyopathy despite early cardiac pacing. Left ventricular function was normal soon after birth in 15 of them. 12 of 16 patients had developed congestive heart failure before 24 months of age. Their biopsies revealed hypertrophy, interstitial fibrosis, and myocyte degeneration [32].

CONCLUSION

The recommendation that can be made to anti-Ro/SSA and anti-La/SSB antibody positive mothers is that serial echocardiography and obstetric ultrasonography should be performed starting from early second trimester. To the pregnant women at high risk such as women with previously affected newborns, it seems necessary to perform weekly monitoring beginning from early second period of gestation and biweekly monitoring between 24-36 weeks. This is crucial for earlier detection of fetal abnormalities, such as premature atrial contractions or moderate pericardial effusions that might precede complete atrioventricular block, ventricular dilatation, mitral valve regurgitation and disrupted cardiac functions (decreased ejection fraction and fractional shortening) that might give us a chance for successful management.

Finally, generally accepted management of affected pregnancies is to initiate dexamethasone/betamethasone and/or IVIG therapy just after diagnosis of fetal AV block and to use maternal sympathomimetic for fetal ventricular rates <50-55 beats/ min. Weekly fetal echocardiograms are done to follow the progress, and an elective delivery by caesarian section is planned at 36 to 37 weeks. If there is evidence of pericardial effusion, ascites, increasing ventricular ectopy, reduced ventricular shortening fraction or AV valve regurgitation; newborns should be delivered at an early stage of the gestation. After birth, aggressive medical management should be coupled with pacing in those infants who do not respond to medical therapies alone.

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