Cardiological Findings of Babies Born to Mothers with Connective Tissue Disease

Bağ Dokusu Hastalığı Olan Annelerden Doğan Bebeklerin Kardiyolojik Bulguları

Kutay SEL[1], Tolga Hasan ÇELİK[2], İlker ERTUĞRUL[3], H. Hakan AYKAN[3], Ahmet ÖKTEM[4], Can AKAL[5], Şule YİĞİT[2], Dursun ALEHAN[3], Murat YURDAKÖK[2], Tevfik KARAGÖZ[3]

[1]Department of Pediatric Cardiology, Ankara Sami Ulus Pediatric Health and Diseases Training and Research Hospital, Ankara, Turkey
[2]Department of Neonatology, Department of Child Health and Diseases, Hacettepe University, Faculty of Medicine, Ankara, Turkey
[3]Department of Pediatric Cardiology, Department of Child Health and Diseases, Hacettepe University, Ankara, Turkey
[4]Department of Neonatology, Ankara Sami Ulus Pediatric Health and Diseases Training and Research Hospital, Ankara, Turkey
[5]Department of Child Health and Diseases, Hacettepe University, Faculty of Medicine, Ankara, Turkey

ABSTRACT

Objective: Cardiac conduction system is affected and heart blocks can be seen in newborns whose mothers have connective tissue disease, especially with systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS). Anti-SS-A (Ro), and anti-SS-B (La) antibodies in the mother's circulation are responsible for this situation. In this study, it was aimed to evaluate the clinical features and long-term follow-up results of babies born to mothers with connective tissue disease in our hospital.

Material and Methods: Patients who were hospitalized in the neonatal intensive care unit between January 2001 and January 2016 due to the diagnosis of SLE, SS or connective tissue disease in their mothers were retrospectively screened, and their demographic and clinical characteristics and electrocardiographic findings were recorded.

Results: A total of 49 babies from 48 mothers were included in the study. The mean age of mothers at birth was 30.8±5.0 years (28-41), the mean gestational week of patients was 35.8±2.5 weeks (28-41), mean birth weight was 2614±680 g (730-3810 g). Ten newborns (20.4%) had 3rd degree atrioventricular (AV) block, and 1 baby had 1st degree AV block. A permanent pacemaker was implanted in five patients in the neonatal period, two of these patients died in the neonatal period. A pacemaker was inserted in a patient who was followed up with AV block in the 6th month. One baby who had no cardiac conduction problem died due to reasons related to prematurity. The mean follow-up period of 46 living babies was 4.6±3.1 (1.2-10.75) years, and the follow-up period of the patients with complete AV block and without a pacemaker was 5.6±2 years.

Conclusion: Complete AV block in the neonatal period is a serious cardiac problem that requires rapid intervention. Expectant mothers with known connective tissue disease should be followed in tertiary care centers and the fetus should be followed closely. It is possible for newborns in need to return to their normal lives by inserting pacemakers.

Key Words: Atrioventricular (AV) Block, Sjögren's Syndrome, Systemic Lupus Erythematosus

0000-0001-5932-7372 : SEL K
0000-0002-1725-0722 : ÇELİK HT
0000-0002-6607-0568 : ERTUĞRUL İ
0000-0001-5136-3977 : AYKAN HH
0000-0001-7209-6732 : ÖKTEM A
0000-0001-6665-3926 : AKAL C
0000-0002-8755-0384 : YİĞİT Ş
0000-0002-1170-8835 : ALEHAN D
0000-0002-1394-4700 : YURDAKÖK M
0000-0002-7680-8183 : KARAGÖZ T

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Correspondence Address / Yazışma Adresi:

Kutay SEL
Department of Pediatric Cardiology,
Ankara Sami Ulus Pediatric Health and Diseases Training and Research Hospital, Ankara, Turkey
E-posta: kutaysel@yahoo.com

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ÖZ

Amaç: Başta sistemik lupus eritematozus (SLE) ve Sjögren sendromlu (SS) olmak üzere annelerinde bağdokusu hastalığı olan yenidoğanlarda kardiyak iletim sistemi etkilenmekte ve kalp blokları görülebilmektedir. Bu durumdan annenin dolaşımındaki anti-SS-A (Ro), anti- SS-B (La) antikorları sorumludur. Bu çalışmada hastanemizde bağ dokusu hastalığı olan annelerden doğan bebeklerin klinik özellikleri ve uzun dönem takip sonuçlarının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Yenidoğan yoğun bakım ünitesinde Ocak 2001 ile Ocak 2016 arasında annelerinde SLE, SS veya bağ dokusu hastalığı tanısı olması nedeniyle yatırılarak izlenen hastalar geriye dönük olarak tarandı, demografik ve klinik özellikleri ile elektrokardiyografik bulguları kayıt edildi.

Bulgular: Çalışmaya toplam 48 anneden 49 bebek alındı. Annelerin doğum sırasında ortalama yaşı 30.8±5.0 yıl (28-41), hastaların ortalama gestasyonel haftası 35.8±2.5 hafta (28-41), ortalama doğum ağırlığı ise 2614±680 gr (730-3810 gr)'dı. On yenidoğanda (%20 .4) 3. derece atrioventriküler (AV) blok, bir bebekte ise 1. derece AV blok tespit edildi. Beş hastaya yenidoğan döneminde kalıcı kalp pili takıldı, bu hastalardan ikisi yenidoğan döneminde yaşamını yitirdi. AV blok ile takip edilen bir hastaya ise 6. ayında kalp pili takıldı. Kardiyak iletim sorunu olmayan bir bebek ise prematüriteye bağlı nedenler ile yaşamını yitirdi. Yaşayan 46 bebeğin ortalama takip süresi 4.6±3.1 (1.2-10.75) yıl, bunlardan AV tam bloklu olup kalp pili takılmadan izlenen hastaların takip süresi 5.6±2 yıldı.

Sonuç: Yenidoğan döneminde görülen tam AV blok hızlı müdahale edilmesi gereken ciddi bir kardiyak problemdir. Bilinen bağ dokusu hastalığı olan anne adayları üçüncü basamak merkezlerde izlenmeli, fetüs yakın takip edilmelidir. Gereken yenidoğanlara kalp pili takılarak normal yaşamlarına dönmeleri mümkündür.

Anahtar Sözcükler: Atrioventriküler blok, Sjögren sendromu, Sistemik lupus eritamatozus

INTRODUCTION

The incidence of a complete congenital atrioventricular block (CCAVB) in surviving newborns is 1/20000 (1). The most common cause is the presence of autoimmune disease in the mother. Complete congenital atrioventricular blocks occur especially in infants born to mothers with systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS) who has anti-SS-A (Ro), anti-SS-B (La), or both, and are the most serious clinic of neonatal lupus syndrome (2). It has been reported that these antibodies also cause inflammatory myocarditis, endocardial fibroelastosis, and late-onset dilated cardiomyopathy (3). On the other hand, only 1-2% of infants of mothers with positive anti-La/SSB and anti-Ro/SSA antibodies have CCAVB, and most infants have normal heart conduction (4). In addition, clinical findings related to autoimmune disease have not yet emerged in most of the mothers who have children with CCAVB, and serological findings are observed in approximately half of them (5).

In this study, short and long-term follow-up results and cardiac findings of babies born to mothers with diagnoses of SLE, SS or connective tissue disease in our hospital were evaluated retrospectively.

MATERIAL and METHOD

Patients who were hospitalized in the neonatal intensive care unit of Hacettepe University İhsan Doğramacı Children's Hospital between January 2001 and January 2016 due to the diagnosis of SLE, SS or connective tissue disease in their mothers were retrospectively screened. Babies with at least one-year follow-up were included in the study. The demographic and neonatal data of the babies, their mothers' diagnoses, presence of antibodies, fetal and transthoracic echocardiographic findings, electrocardiographic (ECG) findings, presence of AV block and permanent pacemaker needs were recorded in the case form. The study was approved by Hacettepe University, Non-Invasive Clinical Research Ethics Committee (17.01.2017/GO 17/39).

RESULTS

A total of 49 (22 girls) babies born to 48 mothers with one twin pregnancy were included in the study. A total of 38 mothers were diagnosed with SLE, 5 mothers with SS, 3 mothers with SLE and SS, 1 mother with SLE and Raynaud, and 1 mother with SLE and rheumatoid arthritis. The mean age of the mothers at the time of delivery was 30.8±5.0 years (28-41), the mean gestational week of the patients was 35.8±2.5 weeks (28-41), and the mean birth weight was 2614±680 g (730-3810). The birth weights of 15 of our patients were below 2500 g (30%) and the gestational ages of 17 patients were below 37 weeks (34%). A total of 5 patients had low birth weight (SGA) for gestational age. The demographic characteristics of the patients in the study are shown in Table I.

Transthoracic echocardiography examinations revealed a ventricular septal defect in one patient, thin patent ductus arteriosus in one patient, and mild pulmonary stenosis in one patient. ECG was taken for all babies after the study. In total, 10 (20.4%) of 49 infants had 3rd degree AV block/ CCAVB and 1 infant had 1st degree AV block (Table II). All patients with CCAVB were diagnosed in fetal echocardiographic evaluation. Hydrops did not develop in any of these patients. Of the 10 patients with AV block, four of the mothers had SS-A (+) alone, and four had both SS-A (+) and SS-B (+). No antibodies were detected in the mothers of the two patients. Serological findings of mothers of newborns included in the study are shown in Figure 1.

A total of 11 patients with AV block in their ECGs underwent 24-hour Holter electrocardiogram examination. Since the mean heart rate of five patients was <55/min, a permanent

Table I: Demographic characteristics of the patients in the study

	All patients (n=49)	CCAVB + (n=10)	Normal cardiac rhythm (n=39)
Mother'sage (years)	30.8±5.0 (28-41)	27.5±3.5	31.7±5.0
Gestation (weeks)	35.8±2.5 (28-41)	35.8±3.7	35.8±2.2
Birth weight (gr)	2614±680 (730-3810)	2495±914	2644±617
Gender (F/M)	22 F / 27 M	4 F/ 6 M	18 F/ 21 M

***M:** male, **F:** female, **CCAVB:** complete congenital atrioventricular block*

Table II: Findings of newborns with AV block

Patient	Gender	Mother'sage (years)	Diagnosis of the mother	Age of gestation	Fetal echocardiography	Birth weight	ANA	SS-A	SS-B	Diagnosis after birth	Followup
1	M	31	SLE	30	Fetal brady cardia, nosign of heart failure	1650 gr	320	-	-	Complete AV block	5.5 y, no complaints
2	M	24	SLE	38	Normal	2950 gr	160	-	-	Complete AV block	6y, no complaints
3	F	27	SLE	37	-	2620 gr	100	-	-	1st degree AV block	3y, no complaints
4	F	32	SLE	28	Fetal AV block, cardiomegaly	730 gr	320	+	+	Complete AV block, external pacemaker	Exitus due to severe prematurity
5	F	24	SS	38	Fetal bradycardia, cardiomyopathy	3400 gr	320	+	+	Complete AV block, permenant pacemaker at 3rd day	6 y, no complaints
6	F	21	SLE	37	CCAVB	2500 gr	1000	+	+	Complete AV block, permenant pacemaker at 1st day	10 y, cardiomyopathy related to pacemaker
7	M	29	SLE	38	CCAVB, no sign of heart failure	3100 gr	160	+	-	Complete AV block, permenant pacemaker at 5th day	9y, no complaints
8	F	30	SS	39	CCAVB, no sign of heart failure	3750 gr	320	+	-	Complete AV block	8 y, no complaints
9	M	30	SLE	37	Cardiomyopathy	2180 gr	160	+	-	Complete AV block, cardiomyopathy	Permenant pacemaker at 6th months
10	M	26	SLE	38	CCAVB, no sign of heart failure	2890 gr	320	+	-	Complete AV block, permenant pacemaker at 1st day	7 y, no complaints
11	M	28	SLE	35	CCAVB, no sign of heart failure	1800 gr	320	+	+	Complete AV block, permenant pacemaker at 1st day	Exitus due to neonatal sepsis

***M:** Male, **F:** Female, **SLE:** Systemic Lupus Erythematosus, **SS:** Sjögren's syndrome, **CCAVB:** Complete congenital atrioventricular block, **Y:** years*

pacemaker was inserted in these patients in the neonatal period. A pacemaker was implanted in a patient who followed up with CCAVB at 6 months.

Three out of 49 patients died in the neonatal period. A patient with CCAVB, born at the 28th week of pregnancy with a weight of 720 g, in the first day of life; a patient with CCAVB, born at the 35th week of pregnancy with a weight of 1800 g, was placed on an emergency pacemaker, but on the 4th day of his life due to neonatal sepsis; a 29-week-old, 1150-g born patient who had no AV conduction problem, whose mother had HELLP syndrome was able to live up to the 12th day of her life due to reasons related to prematurity. The mean follow-up period of the other 46 patients was 4.6±3.1 years (1.2-10.75). No cardiological problem developed in the follow-ups of 4 patients with pacemakers. Holter ECG follow-ups of four patients with CCAVB who did not need a pacemaker because they were asymptomatic had a mean heart rate of >55/min, and the mean follow-up period of these patients was 5.6±2 years.

Of the infants without CCAVB in the neonatal period; AV block didn't develop in the one-year follow-up of the children of 3 mothers with both SS-A (+) and SS-B (+) antibodies, 2 mothers with only SS-A (+) and 1 mother with only SS-B (+) antibodies.

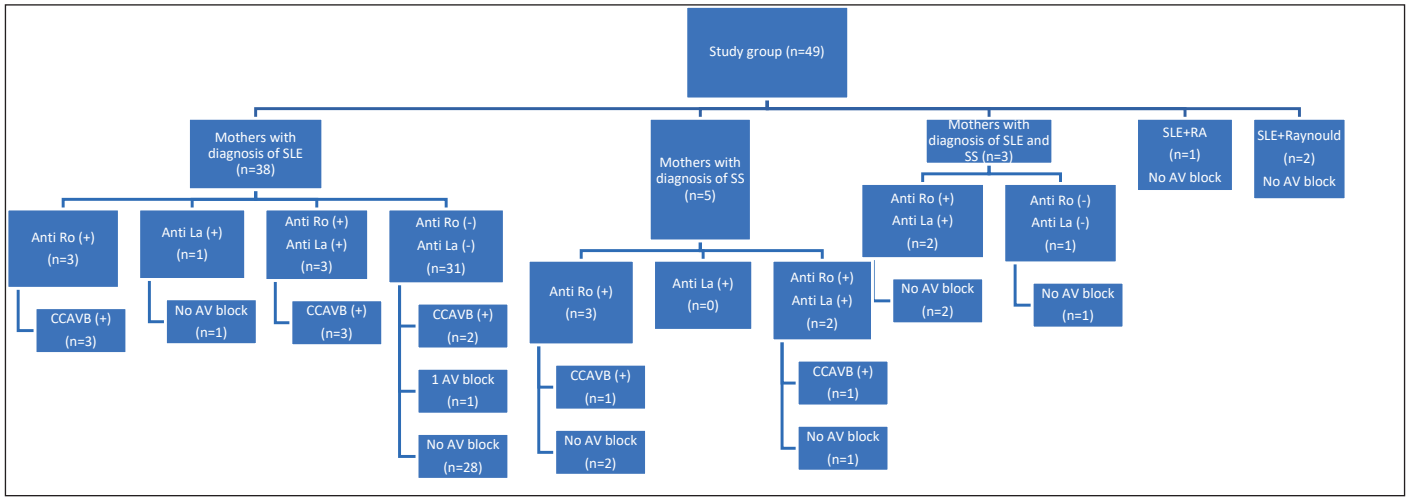

Figure 1: Serological findings of mothers of newborns included in the study.
SLE: Systemic Lupus Erythematosus, ***SS:*** Sjögren's syndrome, ***CCAVB:*** Complete congenital atrioventricular block

AV block was not observed in the babies of 34 mothers who did not have either SS-A or SS-B antibodies. Cardiomyopathy developed in the first year of life in a baby without CCAVB and whose mother was negative for SS-A and/or SS-B antibodies. In the last echocardiography performed at the age of 1.5 years, the ejection fraction was measured as 50%. This patient is being followed up.

In our study, there were five newborns with non-cardiac findings; hepatic enzyme elevation was observed in one newborn, pancytopenia in one newborn and skin findings in 3 newborns.

DISCUSSION

Third-degree AV block is the most serious problem of neonatal lupus. It is irreversible and carries a high risk of morbidity and mortality. In this most serious and life-threatening form called complete block the electrical activity does not pass from the atriums to the ventricles and the ventricles contract independently through a focus from within. Symptoms generally depend on the ventricular rate, which can vary between 30-100/min. The closer the ventricular rate is to the normal mean heart rate for age, the more likely the patient is to be asymptomatic (6). Heart contractility and the ratio of atrial and ventricular rates are also factors affecting the patient's symptomatic. The lower the fetal heart rate during pregnancy, the higher the probability of neonatal heart failure, hydrops, and fetal or neonatal death. This possibility is especially high at ventricular rates below 55/min (7).

All types of heart block can be found in babies born to mothers with lupus. Infants with affected cardiac conduction systems have >80% complete block, other types of the block are less common; second-degree (10-16%) and first-degree blocks (3%) have also been reported (7). In this study, our patients were predominantly 3rd degree AV block (complete block) (90.9%). One patient had 1st degree AV block. In the follow-up of this patient, the PR distance did not shorten, but it did not progress to a more advanced AV block. No such progress has been reported in the literature (8, 9).

It has not been shown that any degree of AV block develops in the future in babies without CCAVB in the neonatal period. In our study, also no block was found in the follow-up in babies who did not have AV block in the neonatal period.

The rate of CCAVB in babies born to mothers with connective tissue disease has been reported to be around 2% (4). In our study, the rate of patients with AV block (20.4%) was found to be higher than that reported in the publications. This can be explained by our hospital is a tertiary reference hospital. All mothers in our study were diagnosed with connective tissue disease. All of our patients with AV block were diagnosed by fetal echocardiography. Fetal hydrops did not develop in any of them. In 5 of these patients, a pacemaker had to be inserted in the neonatal period, since the mean heart rate was below 55/min due to 24-hour rhythm holter evaluation. A permanent pacemaker was implanted in a patient born with CCAVB in the 6th month.

Anti-Ro is the antibody most associated with CCAVB.When antinuclear antibody (ANA) passes from women with active connective tissue disease to the fetus, it damages the fetal thyroid and myocardial conduction system together with anti-Ro/SSA (10,11). While the rate of CCAVB in infants whose mothers have anti-La antibodies alone is less than 1%, it has been reported that the incidence increases up to 5% in infants of mothers with both positive anti-Ro and anti-La antibodies (7,10,12). In our study, 8 of 14 infants whose mothers were positive for one or both of these antibodies had CCAVB (57%). Of the 35 babies whose mothers did not have either of these antibodies, only 2 had CCAVB (5.7%). With these findings, it can be said that the risk of developing CCAVB increases approximately 10 times in babies whose mothers are positive for either or both of these antibodies.

In Sjögren's and mixed connective tissue disease, the risk of CCAVB was found to be higher than in babies of mothers with SLE (3,13). Supporting this finding in our series, two of the five infants whose mothers had Sjögren's syndrome alone had CCAVB (40%), while eight of 38 infants (21%) whose mothers had only SLE had CCAVB.

Criteria for pacing indications have been determined in patients with complete AV block (14). Possible pacemaker implantation risks and complications should be considered when evaluating the indication. Two-thirds of infants with CCAVB require a pacemaker until the first year of life, and this rate reaches 90% until the age of 20 (15). We had five patients who were found to have AV block in the neonatal period but did not need a pacemaker. The patients were followed closely and rhythm holter evaluations were performed intermittently. A pacemaker was implanted in one of our patients when he was six months old. The other four patients were followed up without a pacemaker, as their mean heart rate was higher than 55/min and were clinically and echocardiographically normal.

All of the mothers participating in our study were previously diagnosed with connective tissue disease and were referred to our hospital during pregnancy follow-up. Perinatology follow-ups and fetal echocardiography were performed. It is of great importance for maternal and infant health that these patients are referred to tertiary centers with experienced perinatology, neonatology, pediatric cardiology and pediatric cardiovascular surgery specialists, where they can insert an urgent pacemaker when necessary. More than half of the mothers of newborns with complete atrioventricular block are diagnosed with connective tissue disease later (7). Since the clinical signs and symptoms of connective tissue disease in mothers are often not fully manifested, maternal autoantibodies should be investigated when a complete AV block is detected in the baby.

Apart from heart rhythm problems, it is also reported that 15-20% of babies of mothers with lupus have conditions in which myocardial function is affected such as cardiomyopathy and endocardial fibroelastosis (EFE) (8). These findings can cause severe heart failure and death in infants. In a meta-analysis evaluating a total of 14 studies, EFE was reported up to 20%, even in infants without CCAVB (7). Although the cause is unclear, changes in the fetal immune response are thought to be responsible. Cardiomyopathy developed after one year of age in a patient whose mother had a diagnosis of SLE, had negative anti-Ro or anti-La antibodies, and did not have CCAVB. We thought that this may be due to the mother's SLE or myocarditis in the process.

Problems related to prematurity and intrauterine growth restriction increase the risks of morbidity and mortality in newborns whose mothers have connective tissue disease (7). Fetal-neonatal mortality rates in infants of mothers with lupus are close to 20% (16). Causes of death have been reported as prematurity, hydrops and cardiomyopathy. In our study, three patients (6.1%) died, and all three had prematurity and intrauterine growth restriction. No mortality was detected in the patients followed up after the neonatal period.

Apart from cardiac findings, in babies of mothers with lupus, Sjögren, or mixed connective tissue disorder various findings may occur, including skin findings, liver involvement, and hematological findings. These are often temporary and not life-threatening. The skin lesions and hematological findings usually disappear spontaneously in sixth-ninth month, due to decreasing titer of maternally transmitted autoantibodies in the baby's circulation (17). Among our patients, one newborn had pancytopenia and one had mild hepatic enzyme elevation. Various skin lesions were seen in three patients. All of these non-cardiac findings improved over time.

CONCLUSION

CCAVB seen in newborns is a rare but serious cardiac problem that needs to be well managed because of the potential morbidity and mortality risk. Currently, there is no proven preventive treatment. Therefore, all mothers with known SS-A or SS-B antibody positivity should undergo fetal echocardiography in the early period and require close monitoring with perinatology. Since these pregnant women are at high risk for maternal and infant health, their referral to centers which has pediatric cardiology, pediatric cardiovascular surgery, third-fourth level neonatal intensive care units that can install pacemakers, and planned delivery in these centers are important in decreasing death rates.

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