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Clinical characteristics of neonatal lupus erythematosus

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Neonatal lupus erythematosus is a rare disorder caused by transplacental autoantibodies from the mother to the fetus. This syndrome is characterized by congenital heart block and/or cutaneous lesion. A total of 10 cases of neonatal lupus erythematosus were diagnosed at the National Taiwan University Hospital from 1988 through 1998. The incidence of cardiac anomaly and other clinical features in patients with neonatal lupus erythemayosus in this study was compared with those in previous studies. Results showed that 50% of patients had congenital heart block and/or cutaneous lesion, which is compatible to previous statistics. However, the findings showed that 80% of the patients were female and 90% of the mothers had acquired an autoimmune disorder, which were much higher compared with that of other studies. To date, no definite treatment is suggested prenatally to prevent the occurrence of congenital heart block, but careful maternal screening and serial fetal echocardiogram are warranted.

Key words: Anti-La, anti-Ro, congenital complete heart block, neonatal lupus erythematosus, transplacental autoantibodies

Neonatal lupus erythematosus (NLE) represents the effect of transplacental autoantibodies on the fetus in women with systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), or other autoimmune disorders [1]. Although these autoantibodies do not necessarily reflect clinical condition in the mother, NLE is likely to result from fetal or neonatal tissue damage caused by maternally transmitted immunoglobulin (Ig) G autoantibodies, particularly anti-SSA/Ro and/or anti-SSB/La antibodies [2]. Some reports have shown that over 90% of the affected infants have precipitating anti-SSA/Ro, and over 50% have anti-SSB/La [3].

The major clinical manifestations of NLE involve the skin, liver, blood cells, and cardiac abnormalities along with high titers of autoantibodies. The noncardiac features usually appear postnatally, and often resolve within 6 months after birth, coincident with the clearance of the maternal autoantibodies from the infant's circulation [3]. The most serious and irreversible clinical feature is associated with congenital complete heart block (CCHB), which has an estimated 10% to 30% mortality [1,4]. Significant morbidity (22%-71%) is also documented in patients requiring pacemaker [5]. A fetus is most commonly detected with arrhythmia or bradycardia during the second trimester or as early as in the sixteenth week of gestation [6]. This cardiac injury is presumed to arise from the active transport and deposition of autoantibodies that causes an inflammatory process in the cardiac muscles. Congenital complete heart block is a relatively uncommon disorder, occurring in 1 of every 15 000 to 20 000 live births [7]. It may be an isolated incident or combined with other structural cardiac defects. Although many of these mothers are asymptomatic, women with autoimmune disorders such as SLE or SS are inclined to have affected offspring.

A retrospective study is conducted to assess the clinical conditions of patients given a diagnosis of NLE between 1988 and 1998 in the National Taiwan University Hospital. The diagnoses were based on the criteria established by the Canadian Pediatric Rheumatology Association [1]. The purpose of this study was to ascertain the clinical features, maternal factors, and the cardiac complications of NLE. Data in other studies are collected to compare the clinical features among different races and ethnicities. Results suggested a relatively high incidence of SLE mothers giving birth to NLE children. A collaborative network should be established among pediatricians, obstetricians, rheumatologists, and pediatric cardiologists to develop an adequate healthcare plan and to provide sufficient data to researchers.

Materials and Methods

From January 1988 through August 1998, a total of 10 newborns were found with NLE. The diagnostic criteria included (1) prenatal or postnatal bradyarrhythmia; (2) cutaneous lesions, erythema annulare; (3) hema-

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cytopenia; (4) abnormal liver function; and (5) positive maternal screening for autoimmune disorders (SLE or SS). These infants were either delivered in the National Taiwan University Hospital because of high-risk pregnancy of the mother, or transferred from other local hospitals because of serious clinical condition of the infant.

Data about the patients' sex, maternal factors, and clinical symptoms including cutaneous lesions and cardiac findings were recorded. A complete electrocardiogram (EKG) was performed. Serologic tests included complete blood count, liver function, and immunologic profile of both the mother and the infant including antinuclear antibodies (ANA), Anti-ENA (anti-Ro, anti-La, and Scl-70) antibodies, C3, and C4. Screening for serum autoantibodies to nuclear antigens (ANA) was performed using an indirect fluorescent antibody test system (DiaSorin Inc., Stillwater, MN, US). A double immunodiffusion method was used to detect anti-ENA antibodies (MBL Co., Nagoya, Japan).

Clinical follow-up visit was made by the Pediatric Department with the collaboration of specialists from the Divisions of Cardiology, Rheumatology, and Neonatology.

Results

From January 1988 through August 1998, a total of 10 patients with NLE were enrolled into this study. There were 8 female and 2 male infants, giving a female/male ratio of 4:1. All patients were symptomatic at birth, and 7 of them had arrhythmia bradycardia noted prenatally. Eight of the 10 mothers had been given a diagnosis of SLE, all were either under medical control or subclinical; one mother had a diagnosis of SS. Clinical characteristics of the patients are summarized in Table 1.

Five of the 10 patients manifested with cutaneous lesions at birth. The affected infants were mostly presented with classical annular or elliptical erythematous lesions with or without scaling. The rash was confined to the face in all of these infants. Cardiac anomalies were detected either prenatally or at birth in 8 patients; among them, 5 (50%) had complete heart block, one had second degree atrioventricular block, one had Wolff-Parkinson-White syndrome, and one had suspected myocarditis. Pacemakers were required in 3 patients with complete heart block. Other noncardiac features included hematologic abnormalities in 7 (70%) infants, 5 of whom with anemia, thrombocytopenia in 7, and leukopenia in one. Hepatomegaly was detected in 6 (60%) infants. During the follow-up period, these conditions had gradually resolved and resumed normal status when the infants reached 2 to 3 months of age.

Immunologic profile in these infants showed an 80% positive rate on anti-SSA/Ro and ANA, and a 50% positive rate on anti-SSB/La. Anti-Scl 70 was positive in 60% of patients. C3 and C4 levels were normal in all except 2 patients who had a slightly decreased C3 level. After several months of clinical follow-up visits, these autoantibodies had returned to normal range.

The mortality in this series was 20%. One patient died immediately after birth because of severe heart failure. Another patient died at the age of 3 years. In spite of pacemaker implantation for complete atrioventricular block, the patient died of dilated cardiomyopathy and congested heart failure.

Compared with previous statistics, this study showed a higher female/male ratio, a higher incidence

Table 1. Clinical characteristics of 10 patients with neonatal lupus erythematosus

Case no.	Sex	Maternal factor	Cardiac manifestation	Cutaneous manifestation	Hematologic manifestation[a]	Hepatomegaly	Anti-Ro/ La/ANA	C3/C4	Outcome
1	F	SLE	W-P-W syndrome	+	+	-	+/+	Normal	Survive
2	F	SLE	-	+	+	-	+/+	Normal	Survive
3	M	-	CCHB	-	-	+	+/+	↓ / ↓	Pacemaker
4	M	SLE	-	+	+	-	+/+	Normal	Survive
5	F	SLE	CCHB	+	-	+	+/-	↓ / ↓	Expiredb
6	F	SLE	CCHB with heart failure	-	+	+	-/-	↓ / ↓	Expired
7	F	SLE subclinical	Secondary A-V block	+	+	+	+/+	↓ / ↓	Survive
8	F	SLE	Suspected myocarditis	-	+	+	+/-	↓ / ↓	Survive
9	F	SLE	CCHB	-	+	+	+/+	Normal	Pacemaker
10	F	SS	CCHB	-	-	-	-/-	↓ / ↓	Survive

Abbreviations: SLE = systemic lupus erythematosus; SS = Sjögren's syndrome; W-P-W syndrome = Wolff-Parkinson-White syndrome; CCHB = congenital complete heart block

[a]Including anemia, thrombocytopenia, and leukopenia.

[b]Patient 5 had experienced heart failure despite of pacemaker implantation.

Table 2. Clinical characteristics of neonatal lupus erythematosus in different studies

Study, author (country, year)	No. of cases (F/M ratio)	Congenital heart block (%)	Cutaneous lesion (%)	Hematologic manifestation (%)	Hepatic manifestation (%)	Autoantibody	Maternal status	Mortality rate, %
Liu *et al* (Taiwan, 2001)	10 (4:1)	5/10 (50)	5/10 (50)	7/10 (70)	6/10 (60)	ANA: 80% (+) Ro: 80% (+) La: 50% (+)	SLE: 8/10 SS: 1/10	20
Buyon *et al* [7] (US, 1998)	166 (1:1)	128/166 (77)	35/166 (34)	N/A	N/A	N/A	Ro/La (+): 105/142 (73%)	13
Ng *et al* [15] (Singapore, 1998)	10 (2.3:1)	0/10	10/10 (100)	N/A	2/10 (25)	ANA: 80% (+) Ro: 60% (+) La: 50% (+)	SLE: 4/9 SS: 2/9 High ANA: 2/9	0
Kaneko *et al* [17] (Japan, 1992)	60 (1.6:1)	5/60 (8)	43/60 (72)	6/60 (10)	10/60 (17)	ANA: 83% (+) Ro: 76% (+) La: 61% (+)	ANA: 97% (+) Ro: 78% (+) La: 63% (+)	N/A

Abbreviations: N/A = not available; ANA = antinuclear antibody; SLE = systemic lupus erythematosus; SS = Sjögren's syndrome

of congenital heart anomalies, and a predilection of mothers with autoimmune disorders (Table 2).

Discussion

Neonatal lupus erythematosus is a rare condition first linked to an autoimmune disorder by McCuiston and Schoch [8] in 1954. In the 1980s, Weston *et al* [9] reported the association between NLE and maternal anti-Ro autoantibodies. To date, NLE has an estimated incidence in one of every 12 500 live births, mainly affecting infants of mothers with anti-SSA/Ro and/or anti-SSB/La antibodies [10]. Although NLE is rare, it affects the counseling and treatment plan of any pregnant women with SLE, SS, or other autoimmune diseases.

The most detrimental and permanent damage to infants with NLE is congenital A-V block, which carries a significant mortality and morbidity either in the immediate newborn period or later as a result of pacemaker complications. The noncardiac manifestations of NLE are transient, resolving within the first 6 months of life with the disappearance of maternal autoantibodies from the neonatal circulation. The most serious complication, cardiac involvement, occurs in 50% of cases [6], and is the major cause of death in NLE patients. In most NLE cases, death is resulted from congested heart failure caused by CCHB [11]. In the neonatal period, the mean mortality caused by CCHB is approximately 15%, although some reported as high as 35% [2]. In addition, a further 10% to 20% of patients die from pacemaker complications, suggesting a minimum total mortality of 25% to 35% [2]. This study showed a mortality rate of 20%; one patient died in the immediate newborn period, and one at the age of 3 years because of dilated cardiomyopathy with congested heart failure. Results were consistent with previous studies.

In this study, 6 (75%) of 8 infants with abnormal heart conditions showed positive results for anti-SSA/Ro, and 20% for anti-SSB/La; the Ro antigen is widely distributed in the fetal conduction system and myocardium [1]. These findings, in particular that concerns anti-Ro, implied that the presence of these antibodies may cause inflammatory reaction in the fetal heart, which may lead to maturation delays, fibrosis, calcification, and total destruction of the conduction systems [12]. Recent studies have showed that the highest risk for CCHB appears to be associated with the presence of antibodies to the 52-kD SSA/Ro and the 48-kD SSB/La polypeptide. The role of the 60-kD SSA/Ro is still under debate [13,14].

Erythema annulare is the characteristic cutaneous lesions occur in approximately half of NLE cases. This study showed a 50% occurrence of erythema annulare, which is similar to previous statistics. The skin rash mostly involve the face and the scalp, and are usually annular, erythematous, and sometimes with fine scales or wrinkling. Most children have spontaneous resolution of skin lesions by 6 months after birth, and the autoantibodies become undetectable. The rashes generally leave no permanent scars.

Hematologic abnormalities, particularly thrombocytopenia, have been described [2]. The patients in this study carry not only a high percentage of thrombocytopenia (7/10) but anemia (5/10) as well. Hepatic involvement usually takes the form of neonatal cholestasis with abnormal bilirubin levels and slightly elevated transaminases [15]. In this study, no patient had signs of jaundice, but an increased incidence of hepatomegaly (6/10) was detected.

The incidence of mothers with rheumatic diseases in this study is higher than that in previous reports, and the subsequent pregnancies of these women are of concern. The true incidence of the recurrence of heart block is not known. A previous study conducted by a national registry in the United States showed that of

the 33 women who had subsequent pregnancies after giving birth to a child with congenital heart block, 6 (18%) had another infant with congenital heart block [6]. Although the recurrence rates are low enough to be encouraging with regard to family counseling, they are still 3 times higher than the 1% to 2% estimated rate of heart block in a primigravida with positive antibodies [15].

There is not yet a standarized protocol for the treatment of NLE. Some scholars have suggested that the work-up for an infant suspected to have NLE should include complete blood count and differential count, liver function tests, and autoantibodies of both the mother and the baby including anti-SSA, anti-SSB, ANA, and anti-U1 ribonucleoprotein antibody. In addition, a complete EKG should be performed [16]. The diagnosis of NLE should be suspected in any infant with typical cutaneous lesions or CCHB, especially those whose mothers had autoimmune disorders.

Specific intrauterine treatment for NLE is seldom necessary. Supportive care and serial follow-up sessions seem to be more important. Some studies have suggested the use of plasmapheresis for mothers with positive anti-SSA/Ro or anti-SSB/La, and initiation of dexamethasone at the time of detection of intrauterine bradycardia. This therapy is based on the assumption that CCHB is the result of an inflammatory lesion [2,6]. The effects of these 2 methods, however, are still controversial. It has also been reported that intrauterine cardiac pacing may be life-saving when CCHB is present [1]. Long-term prognosis for individuals with NLE is unknown; there are some rare cases of NLE developing into SLE, but none have been seen among the 10 patients in this study.

In this study, the clinical features, maternal factors, and the cardiac complications of the patients collected during the past 10 years have been described. A more scrutinized maternal screening program would be beneficial to these high-risk infants and to the researchers, and perhaps initiating intrauterine treatment at the time when fetal arrhythmia was detected can lower the mortality rate.

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