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Neonatal Lupus Erythematosus: Clinical Character, Investigation, and Outcome

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Abstract: **Neonatal lupus erythematosus is an uncommon maternal auto-antibody-associated disease characterized by cutaneous, cardiac, hepatic, hematological, neurological, and pulmonary involvement. A retrospective study was performed to review clinical manifestations, investigation results, outcomes of neonatal lupus erythematosus patients and their mothers at the Department of Pediatrics, Siriraj Hospital during 1993 to 2008. Seventeen neonatal lupus erythematosus patients (10 girls and seven boys) were identified. Cutaneous, cardiac, hepatobiliary, and hematological involvement was found in 70.6%, 64.7%, 52.9%, and 35.3% of infants, respectively. Skin lesions were erythematous patches (91.7%), subacute cutaneous lupus erythematosus (50%), petechiae (41.7%), persistent cutis marmorata (16.7%), and discoid lesions (8.3%). Congenital heart block was found in nine cases, and structural abnormalities were found in nine cases. All sera of patients were positive for antinuclear antibodies. Patients (87.5%) showed positive antiRo/SSA, and 50% had positive antiLa/SSB antibodies. Most neonatal lupus erythematosus mothers (64.7%) were asymptomatic. Five mothers were diagnosed with systemic lupus erythematosus, and one mother was diagnosed with mixed connective tissue disease. All maternal sera was positive for antinuclear antibodies and antiRo/SSA antibody. Seven patients required pacemaker implantation. The mortality rate was 11.8%, caused by congestive heart failure and pneumonia. Antinuclear antibody tests should be used as one of the screening tests in mothers or patients suspected of having neonatal lupus erythematosus.**

Neonatal lupus erythematosus (NLE) is an uncommon acquired condition occurring in a small number of infants whose mothers have autoimmune diseases. The disease is caused by the transplacental passage of maternal autoantibodies, most commonly antiRo/SSA and antiLa/SSB antibodies (1,2). The manifestations are usually characterized by cutaneous lesions or cardiac symptoms, or both (3,4). Hematological, hepatobiliary, central nervous, and pulmonary systems may also be involved (2,5–7). The objective of this study was to obtain information of the NLE patients and their mothers in Thailand.

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METHODS

This study proposal was approved by the Siriraj Ethics Committee for human research protection. The retrospective study was performed at the Department of Pediatrics, Faculty of Medicine, Siriraj Hospital during 1993 to 2008. All affected patients diagnosed with NLE were recruited in this study. The available information, including demographic data, clinical manifestations, and results of laboratory investigations, was collected from the hospital medical records of the patients and their mothers. The treatment results and clinical courses of the patients were also determined during follow-up.

For statistical analyses, the SPSS-17 statistical software package was used (Polar Engineering and Consulting, Nikiski, AK). Most of the data are presented as descriptive statistics; minimum, maximum, percentage, mean ± standard deviation, and range.

RESULTS

A total of 17 patients diagnosed with NLE were identified during this period. Ten girls and seven boys were involved yielding a 1.4:1 F:M ratio. Prematurity occurred in 58.8%. The mean gestational age (GA) at delivery was 37 ± 2 weeks, and the mean birth weight was 2,455.6 ± 424.4 g, which was small for GA in 29.4%. Onset of the disease developed in the first month of life in 58.8% of the patients, and the mean age at NLE diagnosis was 54.0 ± 18.4 days (range 28–84). Cutaneous, cardiac, hepatobiliary, and hematological involvement was found in 70.6% (12/17), 64.7% (11/17), 52.9% (9/17), and 35.3% (6/17) of infants, respectively. Clinical data, laboratory features, treatment, and course of the disease in these patients and their mothers are summarized in Table 1.

The cutaneous findings are shown in Table 2. The lesions were distributed on the face (100%) (Fig. 1), scalp (83.3%), trunk (75.0%) (Fig. 2), extremities (66.7%), periorbital area (33.3%), and palm and sole (25.0%). One neonate developed skin lesions after phototherapy. The rashes healed with hypopigmentation, hyperpigmentation, telangiectasia, and mild skin atrophy in patient 3, patient 4, patient 5, and patient 7, respectively. The pigmentary changes faded with time, but telangiectasia and skin atrophy in two cases persisted.

Among 11 cases with cardiac involvement, seven cases (63.6%) developed congenital heart block (CHB) with associated structural abnormalities, two cases (18.2%) had isolated CHB, and two other cases (18.2%) presented with only structural abnormalities. Bradyarrhythmia was detected from the routine ultrasonography during antepartum care in seven patients and after birth in two patients. Severe congestive heart failure resulted in hydrops fetalis in one neonate. The echocardiogram revealed associated structural abnormalities in nine newborns, shown in Table 3. Two patients presented with myocarditis and two patients with dilated cardiomyopathy. Four patients developed only cardiac manifestation, without any other organ systems involvement. Combined cutaneous and cardiac involvement was found in five cases.

Hepatobiliary manifestations were identified in nine out of 17 patients (52.9%). Of these nine cases, all had elevated liver enzymes, six had hepatomegaly, four had jaundice, and four had splenomegaly. Six patients (35.3%) with hematological manifestations had mild anemia 5/6 (83.3%) or thrombocytopenia in 4/6 (66.7%), or both. Some patients with hepatobiliary and hematological manifestations were asymptomatic. The laboratory abnormalities were detected from routine screening.

The sera of NLE patients demonstrated positive antinuclear antibodies (ANA) with a speckled pattern in 16 of 16 patients (100%). Out of these 16 cases, 10 (62.5%) had titers higher than 1:640. AntiRo/SSA was identified in 14/16 (87.5%), and antiLa/SSB was detected in 8/16 (50%). The laboratory results are presented in Table 4. The positive antiRo/SSA, antiLa/SSB, and antiribonucleoprotein (RNP) antibodies in NLE patients did not correlate with any specific clinical presentation.

The mean age of the mothers at the initial diagnosis of NLE in their babies was 27.6 ± 4.3 years old. Most NLE mothers (64.7%) in this study were healthy and asymptomatic at the time when their offspring's illness was identified. Five mothers fulfilled the American College of Rheumatology revised criteria for diagnosis of systemic lupus erythematosus (SLE). Three of these mothers were diagnosed before pregnancy, and the other two developed fully active disease during pregnancy. One mother had been diagnosed with mixed connective tissue disease 3 years before pregnancy. One patient's maternal grandmother had Sjogren's syndrome, and another patient's maternal grandmother had SLE. None of these women had delivered a child with NLE before or after the index case. All 16 maternal sera showed positive ANA with speckled pattern. In 80% of the positive ANAs, the titer was higher than 1:1,280.

Low potency topical corticosteroid was prescribed in 10 cases with cutaneous lesions. Patients with severe hepatic and hematological involvement required oral prednisolone. Methylprednisolone was instituted in one neonate with severe thrombocytopenia. Medications for congestive heart failure were introduced for cardiac symptoms. Seven patients required pacemaker

TABLE 1. *Clinical Data, Laboratory Results, Treatments, and Courses of Neonatal Lupus Erythematosus in the Patients and Maternal Disease*

Patient No.	Sex	Mat diseases	GA (wk)	Involvement				ANA titer	AntiRo	AntiLa	Treatment	Course
				Skin	CVS	Hepatic	Hematologic					
1	M	SLE	40, AGA	–	+	–	–	1:160	+	–	Pacemaker	Good
2	M	–	36, AGA	+	+	–	–	1:2,560	+	+	Topical steroid	Good
3	F	SLE in grandmother	38, AGA	+	–	–	+	1:2,560	+	+	Topical steroid	Good
4	F	Hb E heterozygote	37, SGA	+	+	–	–	1:160	+	+	Pacemaker, CHF Tx, systemic & topical steroid	Improve, CHF Tx, poor wt gain
5	F	SLE	36, SGA	+	–	+	–	1:2,560	–	–	–	Good
6	F	–	36, SGA	–	+	–	–	1:2,560	+	+	Pacemaker	Good
7	M	SLE	39, AGA	+	+	+	+	1:640	+	+	System & topical steroid	Good
8	M	–	38, AGA	–	+	+	–	1:640	+	+	Pacemaker, systemic steroid	Good
9	F	–	36, AGA	+	–	+	–	1:40	+	–	System & topical steroid	Good
10	M	–	39, AGA	–	+	–	–	1:160	+	–	Pacemaker, CHF Tx, systemic steroid	Death
11	M	Sjogren's syn in grandmother	40, AGA	+	–	+	–	1:2,560	NA	NA	Topical steroid	Good
12	F	SLE	36, AGA	+	–	+	+	1:640	+	+	–	Good
13	F	–	32, LGA (Hydrops fetalis)	–	+	–	–	NA	+	–	Pacemaker	Good
14	M	MCTD	36, SGA	+	+	+	+	1:2,560	–	–	Systemic & topical steroid	Good
15	F	–	35, AGA	+	+	–	–	1:40	+	–	Pacemaker, CHF Tx, topical steroid	Death
16	F	SLE	37, SGA	+	–	+	+	1:2,560	+	–	Systemic & topical steroid	Good
17	F	–	38, AGA	+	–	+	–	1:40	+	+	Systemic & topical steroid	Good

GA, gestational age; CVS, cardiovascular; ANA, antinuclear antibody; SLE, systemic lupus erythematosus; AGA, appropriate for gestational age; SGA, small for gestational age; CHF Tx, congestive heart failure treatment; LGA, large for gestational age; NA, not available; MCTD, mixed connective tissue disease.

TABLE 2. *Cutaneous Lesions in 12 Neonatal Lupus Erythematosus Patients*

Lesions (12 patients)	Number of patients	(%)
Erythematous macules and patches	11	91.7
Subacute cutaneous lupus erythematosus	6	50.0
Petechial hemorrhage	5	41.7
Persistent prominent cutis marmorata	2	16.7
Discoid lesion	1	8.3

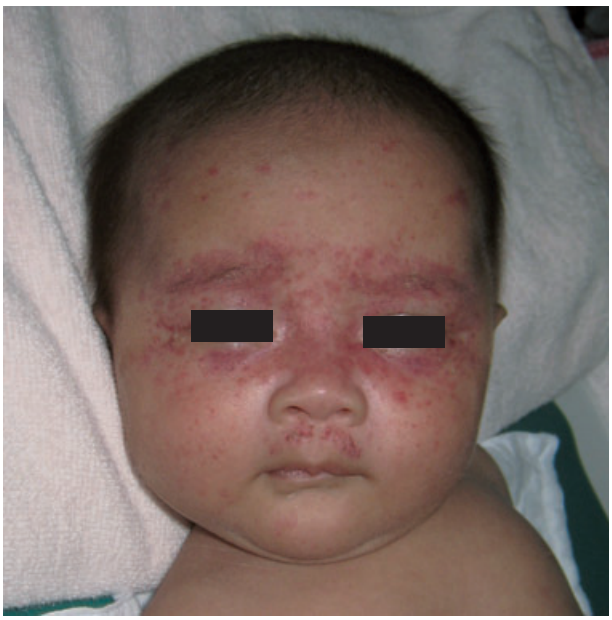

Figure 1. Erythematous confluent macules and patches on face, especially periorbital areas.

implantation, due to heart block with poor cardiac function and refractory congestive heart failure.

The course of the disease was favorable in 14 cases during the mean follow-up period of 47.9 ± 30.6 months (range 4–95). The clinical manifestations in most patients resolved, except for one patient who had poor weight gain and was treated for congestive heart failure treatment. After reevaluation by echocardiogram, all structural heart defects disappeared without any therapy. Two patients in this series died. The first patient died at 29 months old from congestive heart failure and pneumonia. The other, who had severe dilated cardiomyopathy and congestive heart failure, died from *Escherichia coli* pneumonia and septicemia at the age of 9 months after pacemaker revision.

DISCUSSION

Neonatal lupus erythematosus is a disease representing the effect of transplacental autoantibodies on the fetus of

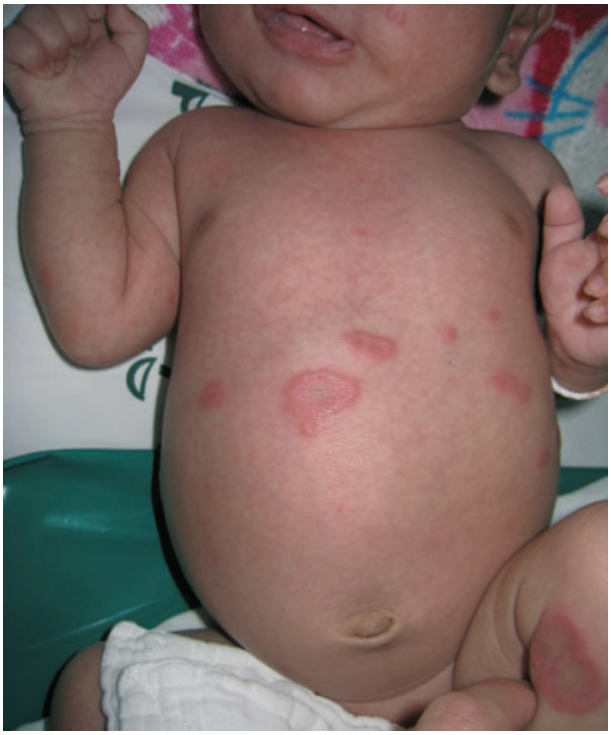

Figure 2. Erythematous annular plaques with fine scales on the trunk.

the mother with SLE, Sjogren's syndrome, or other autoimmune disorders. Maternal antiRo/SSA or anti-La/SSB, or both, and rarely antiU1RNP antibodies cross the placenta and damage the developing fetal tissue, producing transient manifestations in the neonate (7–9). Apart from maternal immunoglobulin G antibodies, environmental factors and fetal genetic components may contribute to the pathogenesis of NLE or amplify the effects of the antibodies, which may be necessary but insufficient in causing the tissue injury.

The incidence of NLE is approximately 1 in 12,500 to 20,000 live births, but the true incidence of NLE is still not defined because of underdiagnosis (2,7,10). Girls are slightly more affected than boys, and the prematurity rate in this report was high, which confirms data from the previous articles.

The clinical features of NLE consist of cutaneous, cardiac, hepatic, hematological, and neurological abnormalities (2,5,6). Cutaneous and cardiac findings are the most common presentations of the disease (3,4). They coexist in 29.4% of cases in this study but infrequently in the same individual as recorded in the national registry of NLE. Other transient features of NLE include aseptic meningitis, myelopathy, and pneumonitis, which were not found in this series. Although many reports showed most NLE infants manifested with a single organ system

TABLE 3. *Details of 11 Neonatal Lupus Erythematosus Patients with Cardiac Involvements*

Cardiac involvements (11 patients)		Number of patients	(%)
Congenital heart block		9	81.8
	Third degree AV block	7	63.6
	Second degree AV block	1	9.1
	First degree AV block	1	9.1
Structural abnormalities		9	81.8
	PDA	4	36.4
	ASD	1	9.1
	Patent foramen ovale	1	9.1
	PDA + ASD	1	9.1
	PDA + patent foramen ovale	1	9.1
	PDA + ASD + patent foramen ovale	1	9.1

AV, atrioventricular; PDA, patent ductus arteriosus; ASD, atrial septal defect.

TABLE 4. *Laboratory Results of Neonatal Lupus Erythematosus Patients and Their Mothers*

	Patients		Mothers	
Test	No. positive/ No. done	(%)	No. positive/ No. done	(%)
ANA	16/16	100.0	16/16	100.0
AntiRo/SSA	14/16	87.5	12/12	100.0
AntiLa/SSB	8/16	50.0	7/12	58.3
AntiRNP	6/10	60.0	3/6	50.0
Anticytoplasmic	1/7	14.3	0/5	0.0
Anticardiolipin	–	–	2/4	50.0
Anti-ds-DNA	1/12	8.3	1/10	10.0
Anti-Sm	0/6	0.0	1/6	16.7
LE	1/5	20.0	3/5	40.0
RF	1/3	33.3	3/3	100.0
Lupus anticoagulant	–	–	0/3	0.0

ANA, antinuclear antibody; LE, lupus erythematosus; RF, rheumatoid factor.

involved (8), our cases demonstrated 23.5% with cardiac involvement as the sole manifestation. All patients with cutaneous lesions had also been observed in association with hepatobiliary or hematological or both involvements. Organ involvement was detected from the screening tests even though some organ involvements were subclinical.

Skin involvement in NLE is common as in previous reports. It may be present at birth, but usually appears a few weeks later. The cutaneous lesions are characterized by erythematous annular or polycyclic plaques with or without fine scales of subacute cutaneous lupus erythematosus (9). The face and scalp are almost always affected, but it can be anywhere on the body, even on nonsun-exposed areas (2,11). The extensive confluent erythema, especially in the periorbital region, may give a "raccoon-eye" or "owl-eye" appearance (8,12).

Although ultraviolet radiation can induce or exacerbate the eruptions in many NLE cases, it is not required for their development (13). It is probably only one of several etiological factors, since NLE can be seen immediately at birth, and lesions can be found on nonsun-exposed areas. Because of the limited opportunity for sunlight exposure in neonates and young infants, photosensitivity is more commonly demonstrated after phototherapy for neonatal hyperbilirubinemia.

Congenital heart block and cardiomyopathy are characteristic manifestations of cardiac NLE (8). The fetus is most commonly detected with arrhythmia or bradycardia during the second trimester or early gestation, so diagnosis of heart block was mostly detected during pregnancy from the routine screening by obstetrical ultrasonography. The transplacentally maternal autoantibody binding to the antigens on the surface of myocytes of the fetus in utero triggers the inflammatory response, causing irreversible fibrotic replacement of the conducting system of atrioventricular node and dilated cardiomyopathy (1,2). The occurrence of associated structural cardiac defects such as atrial septal defect (ASD) secundum and patent ductus arteriosus (PDA) has been commonly reported in NLE infants. It is likely a result from fetal or neonatal tissue damage. In this study, the prevalence of cardiac involvement seems to be higher than in other studies. This may be due to our current practices in antenatal care. Increased use of routine fetal monitoring by ultrasonography may detect more cardiac abnormalities and allow earlier diagnosis. Another reason is the high number of preterm NLE neonates in our study, with higher rates of PDAs recorded, correlating with gestational age.

The clinical variants of hepatic involvement in NLE have been described in the form of conjugated hyperbilirubinemia, elevated liver enzymes, cholestatic hepatitis, and fulminant liver failure. The results of this and some previous studies confirm that NLE have significant hepatobiliary involvement, which may be underdiagnosed or misdiagnosed as physiologic jaundice (5).

Hematological abnormalities, including thrombocytopenia, leukopenia, and hemolytic anemia, are less frequently found in NLE (7). They are generally associated with other manifestations; however, isolated neonatal thrombocytopenia occurs very infrequently as the sole manifestation of the disease and occurred in one of our cases.

The principal serologic characteristics of NLE are antiRo/SSA or antiLa/SSB (or both) maternal autoantibodies (7). Similar to previous articles, antibody to the Ro/SSA protein was present in almost all cases, and antibody to the La/SSB protein was less frequently presented. From our results, positive ANA with speckled pattern was demonstrated in all NLE neonates and their mothers. All mothers had antibodies to the Ro/SSA protein. Antinuclear antibody should be suggested as one of the screening tests in the patient, mother, or both if the patient was suspected NLE.

Autoantibody to the Ro/SSA protein complex responsible for the development of CHB is present in virtually all cases of NLE with associated CHB. Positive antiU1RNP is usually associated with atypical cutaneous lesion without cardiac or systemic abnormalities in a small number of NLE and may play a role in the pathogenesis of thrombocytopenia. Because of the limitation of being a retrospective study, not all necessary data and investigations were obtained in this study. All NLE with cardiac involvement had maternal positive antiRo/SSA. AntiLa/SSB and antiRNP did not show any correlation with cutaneous manifestation or thrombocytopenia. The association of the maternal or patient autoimmune serologic markers and clinical manifestations were not demonstrated. The reasons why some babies develop skin disease, while others develop heart disease, are still not established. The tissue injury may depend on multiple factors, which have not yet been completely elucidated.

The manifestations of lupus erythematosus in the mothers are very different from their babies. Most women are asymptomatic when their infants are diagnosed with NLE, while the remaining women have SLE, Sjogren's syndrome, rheumatoid arthritis, or undifferentiated connective tissue disease (2,3,8,10). The finding of maternal grandmothers of NLE patients having SLE and Sjogren's syndrome in this review is the evidence supporting the pathogenesis of genetic autoimmune connective tissue disease predisposition of NLE.

The diagnosis of NLE is usually established by compatible features together with the presence of NLE-associated autoantibodies in maternal or infant serum. Low potency topical corticosteroids and sun protection are the mainstays of therapy for treatment of cutaneous NLE. Persistent telangiectasia can be treated with a vascular laser. Standard medical management is required for congestive heart failure in cardiac NLE. Pacemaker implantation is frequently necessary for NLE babies who are unable to compensate for a slow heart rate. Hepatic and hematological manifestations may be treated with systemic corticosteroids, intravenous immunoglobulin (IVIG), immunosuppressive agents, or all (8,12). Other therapeutic options such as plasmapheresis in severe cases may deplete the antibodies from the circulation. Systemic corticosteroids, IVIG, plasmapheresis, and immunosuppressant have been attempted in symptomatic mothers to prevent or reduce the prevalence of NLE with variable success.

The cutaneous lesions and other noncardiac manifestations of NLE are transient and disappear spontaneously within weeks or 6 to 8 months after birth when maternal autoantibodies disappear from the infant's circulation (9,10). The lesions may occasionally leave residual dispigmentation, persistent telangiectasia, and rarely atrophic scars at affected areas (11,13). Recently Boros et al (14) highlighted hydrocephalus and macrocephaly as part of the spectrum of central nervous system manifestations of NLE. While none of our patients were diagnosed with this, a limitation of the study is that they were not specifically evaluated for this.

Multiple factors have been identified in association with the poor outcome. The most serious irreversible permanent structural cardiac changes, such as congenital conduction defect, cardiomyopathy, and endomyocardial fibroelastosis, determine the NLE mortality, which is estimated at about 10% to 30% (3,4). Death mostly results from congestive heart failure caused by complete CHB. In this report, the prognosis of the clinical outcome of NLE was also determined by the severity of cardiac manifestations. Children who had NLE may be expected to have increased risk to develop autoimmunity later in life (10,11,15).

The diagnosis of NLE should be suspected in any neonate with CHB, typical cutaneous lesions, or with both, particularly those whose mothers had autoimmune disorders. Careful long-term monitoring of these infants and their mothers is necessary to determine any sequelae, because evidence of autoimmune diseases developing later exists.

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