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Neonatal Lupus Erythematosus in South Korea: Clinical and Serologic Features

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Abstract

Background: Neonatal lupus erythematosus (NLE) is an autoimmune disease associated with maternal anti-SS-A/Ro and anti-SS-B/La antibodies and characterized by cutaneous erythema, congenital heart block (CHB), hepatic dysfunction, and hematological abnormalities.

Aim: This study aimed to identify the clinical characteristics of cases of NLE among South Koreans by analysis of data reported in the literature and in the medical records of 1 NLE patient at our hospital and compare them to the clinical characteristics of NLE among Caucasians, as reported in the literature.

Methods: The clinical data regarding 1 patient diagnosed with NLE at our hospital and those of 19 patients diagnosed with NLE at other South Korean hospitals between 1993 and 2010 were reviewed and analyzed before being compared with those regarding Caucasians diagnosed with NLE, as reported in the literature.

Results: Regarding onset of manifestation, 80% of NLE patients in South Korea began to display clinical characteristics of NLE within 4 weeks of diagnosis. Regarding the form of clinical manifestation, 80% manifested skin abnormality; 25%, CHB; 35%, hematologic abnormality; and 25%, transient elevated transaminase level. These percentages were comparable to those reported for Caucasian NLE cases. Whereas the literature indicates a female predominance in NLE incidence among Caucasians, analysis of the study data indicates a male predominance in NLE incidence among South Koreans.

Conclusions: Other than that for CHB, the incidence of each form of NLE manifestation is relatively similar for South Korean and Caucasian NLE cases. The major difference between the incidence of NLE between South Koreans and Caucasians concerns the male:female ratio, which appears higher for South Koreans, and to indicate a male predominance in NLE incidence among South Koreans.

Keywords: Anti-La/(SS-B) antibody; Anti-Ro/(SS-A) antibody; Anti-U1RNP antibody; Congenital heart block; Neonatal lupus erythematosus

Introduction

Neonatal lupus erythematosus (NLE) is a rare disorder first described by McCuiston and Schoch [1]. Based on the finding that more than 95% of infants with NLE test positive for anti-Ro/(SS-A) and/or anti-La/(SS-B) antibodies, the route of NLE transmission is hypothesized to be transplacental passage of maternal antibodies, especially anti-Ro/(SS-A) and/or anti-La/(SS-B) antibodies. Mothers of affected infants may display overt symptoms of a connective tissue disorder, such as lupus erythematosus or Sjogren syndrome, or be completely asymptomatic. Although NLE patients usually develop transient lupus dermatitis or are found to have congenital heart block (CHB), those experiencing the former have an excellent long-term prognosis if skin lesions are the sole manifestation, and those experiencing the latter have a good long-term prognosis if the heart block is successfully treated [2].

Although NLE appears to be a rare disorder, its true incidence may be much higher because of a suspected high rate of undiagnosed cases. It is therefore important to identify infants at risk for developing this disease early in the gestation period. To aid in this effort, this study analyzed the clinical characteristics and outcomes of 19 cases of NLE reported in the South Korean literature between 1993 and 2010 and of 1 case diagnosed at our hospital and compared the findings with those regarding cases of NLE among Caucasians, as reported in the literature.

Material and Methods

To identify 19 cases of NLE in South Korea that had been reported in the literature, a journal review was conducted. Although the 19 case reports selected for analysis did not describe the means of serologic testing, they described the results for each case. After review of the data contained in these case reports and those in the medical records of 1 case of NLE at our hospital, the findings regarding symptom onset, patient sex, antibody status, and characteristics of each form of clinical manifestation were summarized and compared with the findings regarding NLE among Caucasians, as reported in the literature.

Results

The following sections describe the findings from the review and analysis of the data regarding 20 cases of NLE in South Korea [3-20], including those regarding symptom onset; patient sex; antibody prevalence; and clinical manifestation of cutaneous, cardiac, hematological, and hepatobiliary abnormality (Table 1).

Symptom onset

Clinical manifestation of NLE was found to begin at birth in 5 cases (25%), by 4 weeks in 11 cases (55%), and after 4 weeks in 4 cases (20%). Comparison of these findings with the finding that clinical manifestation

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	Sex	Onset of symptoms (days after birth)	Cutaneous lesion	Site	ANA profile					ECG	CBC/LFT
					Titer	Anti-dsDNA	Anti-Ro	Anti-La	Anti-U1RNP		
Kim et al. [3]	M	30	AE	Face	1:40	+	+	-	-	CHB	NL
Chu et al. [4]	M	1	AE	Face	+	+	+	+	-	CHB	PLT 69,000 AST/ ALT 336/591
Lee et al. [5]	F	14	AE	Face	1:160	NP	-	+	NP	NL	NL
Choi et al. [6]	M	60	None	None	+	+	+	-	-	NL	NL
Kim et al. [7]	F	1	None	None	+	-	+	+	-	CHB	NL
Shin et al. [8]	M	30	AE	Face, ext	+	+	+	+	+	NL	Hb 7.5 AST/ALT 131/871
Park et al. [9]	M	1	AE	Face	+	+	+	+	-	NL	Hb 13.8 PLT 37,000
Chung et al. [10]	M	1	None	None	+	-	+	+	-	CHB	NL
Kwon et al. [11]	F	4	AE	Entire body	+	-	+	+	NP	NL	NL
	M	5	AE	Face, ext	+	-	+	+	NP	NL	NL
Oh and Lee [12]	M	30	AE	Face, trunk	1:2,560	-	-	-	+	NL	Hb 9.2
Noh et al. [13]	M	14	Target-like	Face, ext	1:320	-	+	+	NP	NL	NL
Jung et al. [14]	M	1	None	None	+	+	+	+	-	CHB	NL
Chung and Chey [15]	F	28	AE	Face, ext	+	NP	+	+	NP	NL	Hb 9 AST/ALT 137/150
Ahn et al. [16]	F	21	AE	Entire body	1:80	-	-	-	+	NL	NL
Hong et al. [17]	M	3	Target-like	Entire body	1:80	+	+	+	-	NL	NL
Lee et al. [18]	M	15	Papule	Entire body	+	+	+	+	-	NL	Hb 7.2 AST/ALT 110/73
Park el al. [19]	M	21	AE	Face, ext	1:160	-	-	+	NP	NL	NL
Kim and Yoon [20]	F	7	AE	Face, ext	1:320	-	+	+	NP	NL	Hb 8.3 AST/ALT 75/112
Case in this study	M	20	AE	Face, ext	1:640	+	+	+	NP	NL	NL

AE: annular erythema; ALT: alanine aminotransferase; ANA: antinuclear antibody; AST: aspartate aminotransferase; CBC: complete blood count; CHB: congenital heart block; ECG: electrocardiogram; Ext: extremity; Hb: hemoglobin; LFT: liver function test; NL: normal; NP: not performed; PLT: platelet

Table 1: The clinical and serologic features of the reported cases of neonatal lupus erythematosus in the south Korean literature.

Authors	Sex	Average age of detection (weeks gestation)	Complete or incomplete CHB	Type of treatment	Heart rate at birth	Other findings
Kim et al. [3]	M	36 weeks gestations	Complete	Conservative	Not described	
Chu et al. [4]	M	25 weeks gestations	Incomplete	Conservative	42-87/min	
Kim et al. [7]	F	36 weeks gestations	Complete	Temporary insertion of pacemaker at birth	52/min	Moderate patent ductus arteriosus, patent foramen ovale
Chung et al. [10]	M	33 weeks gestations	Complete	Conservative	60-70/min	
Jung et al. [14]	M	32 weeks gestations	Complete	Conservative	<70/min	A 2-day old patient died of bradycardia from heart failure

Table 2: Clinical features of 5 NLE cases with CHB.

of NLE begins within 4 weeks for the majority of Caucasians indicates that symptom onset generally begins within the same timeframe for South Korean and Caucasian NLE patients.

Sex

Among the patients examined in this study, 14 (70%) were male and 6 (30%) were female, indicating a tendency toward male predominance in NLE incidence among South Koreans. In contrast, analysis of the data regarding NLE incidence among Caucasians indicates a female predominance [21,22].

Antibody prevalence

Most cases tested positive for anti-SS-A/Ro antibody, anti-SS-B/La antibody, or both forms of antibodies. Specifically, 2 cases (10%) tested positive for anti-SS-A/Ro antibody alone, 2 (10%) for anti-SS-B/La antibody alone, 14 (70%) for both anti-SS-A/Ro and anti-SS-B/La antibodies, and 2 (10%) for neither anti-SS-A/Ro nor anti-SS-B/La antibody. Although this last group tested positive for neither anti-SS-A/Ro nor anti-SS-B/La antibody, it did test positive for anti-U1-RNP antibody. Although all 20 mothers tested positive for the same antibody as did their infants, 12 mothers (60%) were asymptomatic, whereas 8 (40%) had been diagnosed with systemic lupus erythematosus prior to NLE diagnosis.

Cutaneous abnormality

The characteristic cutaneous lesions manifested in most cases of NLE were annular-polycyclic erythematous plaques (Figure 1). Among the 16 cases (80%) found to have developed these lesions, only some were observed to manifest other NLE symptoms. The face and head were found to be the most frequent sites of erythema, with lesions at these sites affecting 12 patients (75%), followed by the extremities and the trunk, with lesions at these sites affecting 7 (44%) and 1 patients

Organ system	Forms of manifestation
Cutaneous	Subacute cutaneous lupus-like lesions, telangiectasia
Cardiac	Heart block, cardiomyopathy
Hepatobiliary	Liver failure, cholestasis, elevated transaminase level
Hematologic	Thrombocytopenia, neutropenia, other cytopenias

Table 3: Major forms of NLE manifestation.

Clinical situation	Treatment
Third-degree block, no hydrops fetalis	Evaluation by serial echocardiography; no therapy.
Second-degree block or alternating second/third-degree block	Administer 4 mg of oral dexamethasone daily. If progression to third-degree block occurs, taper dexamethasone dosage to discontinuation. If reversal to NSR or lesser forms of block occurs, continue to delivery at term.
Prolonged mechanical PR interval (first-degree block)	Repeat echocardiography in 24 h. If first-degree block persists, administer 4 mg of oral dexamethasone daily. If progression to third-degree block occurs, taper dexamethasone dosage to discontinuation. If reversal to NSR occurs or first-degree block persists, taper or individualize therapy.
Block associated with signs of myocarditis, CHF and/or hydropic changes	Treatment with 4 mg of oral dexamethasone daily until improvement.
Severely hydropic fetus	Consider termination. Treatment with 4 mg of oral dexamethasone daily and apheresis to rapidly remove maternal antibodies.

CHF: chronic heart failure; NSR: normal sinus rhythm

Table 4: Therapeutic approaches to CHB diagnosed in utero.

(6%), respectively. In 4 patients (25%), erythema was described as having spread over the entire body. The lesions were reported to have typically disappeared spontaneously and without any remnant pigmentation within several months, in parallel with the disappearance of serum antibodies. Use of topical corticosteroids was reported helpful in some cases.

Cardiac abnormality

The primary cardiac manifestation of NLE has been reported to be CHB. This finding is consistent with those of this study, which found that 5 patients (20%) had been diagnosed with CHB, all of whom had been diagnosed before birth. Regarding the incidence of CHB and other forms of NLE manifestation, 1 patient (5%) had been diagnosed with NLE and CHB in the absence of cutaneous abnormality and 4 (20%) with CHB and erythema. Regarding CHB severity, 4 patients (20%) had been diagnosed with complete CHG and 1 (5%) with incomplete CHB (Table 2). In South Korea, the incidence of NLE patients diagnosed with CHB alone is less than 50%, compared to a rate of greater than 50% among Caucasian NLE patients diagnosed with CHB alone [23].

Hematological abnormality

Hematological abnormalities were observed in 7 patients (35%). These abnormalities took the form of anemia in 5 patients (20%), thrombocytopenia in 1 (5%), and pancytopenia in 1 (5%) and were found to accompany other forms of NLE manifestation in all these patients.

Hepatobiliary abnormality

Hepatobiliary abnormalities, all of which pertained to elevated transaminase levels, were observed in 5 patients (25%) and found to accompany other forms of NLE manifestation in all these patients.

Discussion

NLE, a rare disease whose true incidence has not yet been determined because of the suspected high rate of undiagnosed incidence, is primarily characterized by clinical manifestation of transient cutaneous lesions, isolated CHB, or both and associated with a variety of systemic manifestations (Table 3). NLE was first described by McCuiston and Schoch in a case report of an infant with transient lupus skin lesions whose mother was found to be ANA-positive [1]. The first case of NLE in South Korea was reported in 1993 [3].

Since its initial identification, clinical manifestations of NLE have been reported to either be present at birth or appear at a mean age of 6 weeks [24]. In South Korea, clinical manifestations of NLE have been found to begin within 4 weeks of birth in 80% of all cases. Analysis of the data in this study indicates a male predominance in NLE incidence among South Koreans, specifically a male:female ratio of 1:0.43. Although a tendency toward male predominance was also found by Lee [21], Buyon [22] and James [25] identified a female predominance. The potentially male predominance of NLE incidence adds to the evidence that women with systemic lupus erythematous are more likely to produce sons compared to women without this condition.

Skin lesions were observed in nearly 95% of all NLE infants investigated in this study. The disappearance of these skin lesions was found to parallel the disappearance of autoantibodies of maternal origin, typically within 6 months after birth. Previous research has found that skin lesions may be apparent at birth but that they more typically appear within the first few weeks after birth, manifesting as an annular or polycyclic erythematous plaque, the characteristic cutaneous lesion observed among cases of subacute cutaneous lupus erythematosus [26]. Although individual annular lesions are typically approximately only 1 cm in diameter, they are often accompanied by extensive confluent erythema, especially around the eyes, giving a "raccoon-eye" or "owl-eye" appearance [27]. Lesions almost always develop on the head, and often on the trunk and extremities. In many children, lesions result from or are exacerbated by sun exposure.

The most severe form of NLE manifestation is cardiac abnormality, specifically CHB, which, as opposed to other forms of manifestation, tends to remain a life-long complication. Fortunately, CHB is very rare, being observed in only 1 of 20,000 births (incidence, 0.005%). Analysis of the data in this study identified a substantial difference in the incidence of CHB between Caucasians and South Koreans. Whereas previous research has indicated that the incidence of CHB among Caucasians with NLE is more than 50% [23], the findings of the present study indicate a much lower incidence of CHB among South Koreans with NLE. More than 80% of all cases of CHB in this study

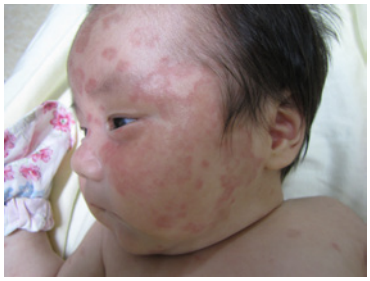

Figure 1: Erythematous and annular plaques on the face.

were detected before 30 weeks of gestation, with a peak incidence of detection occurring at 20 to 24 weeks.

Previous research has found that Infants diagnosed with CHB have a 15% incidence of mortality before 3 months of age and that even beyond the newborn period, up to 10% of NLE patients may develop late cardiomyopathy [28]. More than 65% of surviving newborns, who have an 80% cumulative probability of survival at 3 years, have been found to require pacemakers. For these reasons, various therapeutic approaches are currently being tested for the treatment of prenatally diagnosed CHB patients (Table 4) [29].

Although hematologic and hepatic abnormalities are observed in some cases of NLE, they are generally uncommon. Although thrombocytopenia has been noted in approximately 10% of NLE cases presenting with other forms of NLE manifestation, it typically occurs very infrequently as the sole form of NLE manifestation and is usually transient and unproblematic [30]. In this study, 7 patients (35%) were found to have experienced hematological abnormalities, including pancytopenia, thrombocytopenia, and anemia but all had recovered from these abnormalities within several weeks, as determined by testing that indicated a normal blood cell count level. Previous research has identified hepatobiliary involvement in approximately 10% of NLE cases presenting with other forms of NLE manifestation [31]. Unlike cutaneous and cardiac abnormality, hepatobiliary abnormality appears to occur infrequently as the sole form of NLE manifestation. Among the cases in this study, 25% were reported to have experienced a transient elevation of transaminase levels.

Maternal anti-SSA/Ro or anti-SSB/La antibodies are associated with forms of NLE manifestation, particularly CHB, which in turn may be associated with severe endocardial fibroelastosis (EFE) and dilated cardiomyopathy (DCM) [32]. Tissue injury in the fetus is presumed to depend on neonatal Fc-receptor-mediated transplacental passage of maternal IgG autoantibodies. As disease in the offspring appears to parallel the presence of maternal antibodies in fetal and neonatal circulation, it appears to disappear, except for the cardiac injury resulting from the disease process, with the clearance of maternal antibodies by the eighth month of postnatal life [33]. Previous research has shown that in 95% of NLE cases, the associated autoantibody is anti-Ro/SSA; other associated antibodies include anti-La/SSB and anti-U1RNP [34]. In the present study, anti-Ro/SSA antibody, anti-La/SSB antibody, or both were detected in 18 cases and anti-U1RNP antibody alone in only 2 cases. Among the NLE cases with CHB, all (100%) tested positive for anti-Ro/SSA antibody, and among the 16 with NLE-related skin abnormality, 12 (75%) tested positive for anti-Ro/SSA antibody. These findings strongly support the hypothesis that the development of maternal autoantibodies in reaction to the presence of Ro/SSA and La/SSB antibodies is directly involved in the pathogenesis of NLE. Therefore, for all pregnant women who have anti-SSA/Ro-SSB/La antibodies, serial fetal echocardiography should be performed by an experienced pediatric cardiologist, weekly from 16 to 26 weeks and every other week until approximately 34 weeks [35].

Comparison of the findings of this study regarding South Korean NLE cases with those regarding Caucasian NLE cases indicate that the incidence of each form of NLE manifestation appears similar for South Koreans and Caucasians, except for the incidence of CHB, which appears to be higher among Caucasians. Apart from CHB incidence, the primary difference between NLE incidence in South Koreans and Caucasians appears to be the male:female ratio, with the incidence among South Koreans displaying a male predominance.

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