**Neonatal lupus erythematosus in Japan: a review of the literature**

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**Abstract**

Neonatal lupus erythematosus (NLE) is an autoimmune disease associated with maternal anti-SS-A/Ro and anti-SS-B/La antibodies. NLE is characterized by cutaneous erythema, congenital heart block (CHB), hepatic dysfunction and hematological abnormalities. CHB is irreversible, usually requiring a pacemaker, but other symptoms are reversible and most disappear within 6 months in parallel with declining antibody levels. In Japan, 193 cases of NLE were reported between 1971 and 2008. Most showed erythema, and only 23% of cases presented with CHB. Conversely, antibody status had not been examined in many infants presenting with CHB during the same period. Most pregnant woman with anti-SS-A/Ro and anti-SS-B/La antibodies are asymptomatic, and antibody status is first indicated when their child shows symptoms of NLE. These women show a greater risk of delivering an infant with CHB than normal. CHB is important because the main morbidity and mortality of NLE is from CHB. All clinicians should be familiar with the characteristics of NLE. We believe all pregnant women should be screened for anti-SS-A/Ro and anti-SS-B/La antibodies.

**Key Words:** neonatal lupus; congenital heart block; anti-SS-A/Ro antibody; anti-SS-B/La antibody

**Take-Home messages**

- Neonatal lupus erythematosus (NLE) is an autoimmune disease associated with maternal anti-SS-A/Ro and anti-SS-B/La antibodies.
- The major manifestations are cutaneous annular erythema and congenital heart block (CHB). Minor manifestations include hepatic dysfunction and hematological

abnormalities.

- Many mothers are asymptomatic when NLE is diagnosed.
- The main morbidity and mortality of NLE is from CHB.
- In Japan, infants with CHB may miss being diagnosed with NLE. That causes differences in the incidence of CHB between Japanese and Caucasians.
- All pregnant women should be screened for anti-SS-A/Ro and anti-SS-B/La antibodies.

**Contents**

## 1. Introduction

Neonatal lupus erythematosus (NLE) is an autoimmune disease associated with maternal anti SS-A/Ro and anti-SS-B/La antibodies. NLE is characterized by cutaneous erythema, congenital heart block (CHB), hepatic dysfunction, hematological abnormalities. CHB is irreversible and usually requires pacemaker implantation, whereas the other symptoms are reversible and typically disappear within 6 months, in parallel with declining antibody levels[1].

In Japan, 193 cases of NLE were reported in the literature between 1971 and 2008. We summarize and review the frequency of each manifestation in Japan.

## 2. Materials and methods

We searched journals published from 1971 to 2008 for case reports and reviews dealing with NLE in Japan. We summarized the onset of symptoms, sex, antibody status, and characteristics of each manifestation and made comparisons with data for Caucasians.

## 3. Results

We identified 193 cases of NLE in Japan. Various manifestations were reported, including cutaneous, cardiac, hepatobiliary and hematological abnormalities (Table 1).

### 3.1 Onset of symptoms

Diagnosis of NLE was made at birth in 24 cases (12%), by 2 weeks old in 47 cases (24%), between 2 and 4 weeks old in 54 cases (28%), and after 4 weeks old in 16 cases (8%). Time of diagnosis was unknown in the remaining 52 cases (28%). Most cases

were diagnosed within 4 weeks, similar to results for Caucasians.

### 3.2 Sex

Patients were male in 67 cases (35%), female in 84 cases (43%), and unknown in the other 42 cases (22%). A tendency toward a female predominance was thus apparent in Japan, as seen for Caucasian data[2].

### 3.3 Antibody prevalence

Most cases of NLE showed anti SS-A/Ro antibody, anti SS-B/La antibody or both. Anti-SS-A/Ro antibody alone was seen in 62 cases (32%), anti-SS-B/La antibody alone in 7 cases (4%), both anti-SS-A/Ro and anti-SS-B/La antibody in 94 cases (49%), and neither anti-SS-A/Ro nor anti-SS-B/La antibody in 8 cases (4%), which displayed anti-U1-RNP antibody. Antibody status was unknown in the other 22 cases (11%). Despite displaying the same antibody as the infant in each case, 160 mothers were asymptomatic, with only 27 cases (16.8%) displaying Sjögren syndrome, systemic lupus erythematosus, or mixed connective-tissue disease (MCTD) before NLE was diagnosed. In Japan, 3 cases of NLE associated with maternal hyperglobulinemic purpura have been reported[3-5].

### 3.4 Cutaneous manifestations

The characteristic cutaneous lesions are annular-polycyclic erythematous plaques (Fig. 1). These lesions were seen in 165 cases (85%) with or without other findings of NLE. The location of erythema was only described for 123 cases, so the frequencies of various sites of erythema were compared using only these 123 cases. The face and head

were the most frequent sites of erythema, with 111 cases (90%). The trunk and extremities were also commonly affected, with 82 cases (67%) and 49 cases (40%), respectively. In some cases, erythema had spread over the entire body.

Most cases developed erythema about 2 weeks after birth, and few presented with cutaneous lesions at birth. Lesions typically disappeared spontaneously and without any remnant pigmentation within several months, in parallel with the disappearance of serum antibodies. Use of topical corticosteroids was helpful in some cases. Few cases of persistent telangiectasia, atrophy or pigmentation have been encountered,[6] as in Caucasians[7-9].

### 3.5 Cardiac manifestations

A total of 28 infants (15%) were diagnosed with NLE with CHB in the absence of cutaneous manifestations. Another 15 cases (8%) presented with CHB and erythema. In Japan, the incidence of CHB is <50%, differing from the rate in Caucasians of >50% showing CHB alone[10]. The presence of both cardiac and cutaneous NLE in about 10% of cases is seen in both Japanese and Caucasians patients, although a previous report from Japan showed both cardiac and cutaneous NLE in only 3%[11].

One Japanese case presented with heart failure without atrioventricular block, representing a rare case[12].

The mechanisms underlying CHB involve the deposition of antibodies into the atrioventricular conduction system according to autopsy data[13,14].

### 3.6 Hematological manifestations

Hematological abnormalities with other findings of NLE were seen in 28 cases (14%).

These comprised pancytopenia in 2 cases, thrombocytopenia in 15 cases, anemia in 6 cases and thrombocytopenia and anemia in 1 case. 5 cases of hypocomplementemia have been reported in Japan[15-19].

### 3.7 Hepatobiliary manifestations

Hepatobiliary problems were seen in 47 cases (24%) along with other findings of NLE. Most commonly, cases showed only elevated transaminase levels. One case of NLE with CHB showing severe cholestatic hepatitis has been reported in Japan[20].

### 3.8 Other manifestations of NLE

Four cases presented with hydrocephalus[21,22], two cases presented with fever[23], and two cases presented with gastrointestinal bleeding without low platelet levels[24,25]. Similarly, few such cases have been reported in Caucasians.

## 4. Discussion

NLE was first described by McCuistion and Schoch in a case of transient lupus skin lesions occurring in a baby with an ANA-positive mother.[9] In Japan, the first case of NLE was reported in 1971[26]. The major manifestations are cutaneous and cardiac, with minor hepatic and hematological manifestations. Caucasians and Japanese seem to show no differences in the incidence of each manifestation other than CHB. Few cases have presented with neurological abnormalities and gastrointestinal problem such as hydrocephalus or gastrointestinal bleeding, for which the underlying mechanisms remain unclear.

The risk of having a baby with NLE among unselected anti-SS-A/Ro antibody-positive

women is about 1-2%[27]. The risk of having a second baby with NLE among women who have already had a baby with NLE increases to 15%[28].

CHB was first described by Morquio in 1901[29], and Hogg was the first to point out the association with connective tissue disease in the mother[30]. CHB is very rare, occurring in only 1/20,000 births (0.005%). The most common causes of CHB are significant cardiac abnormality unrelated to maternal abnormalities, and NLE, which is associated with maternal autoantibodies.

The present study found a substantial difference in the incidence of CHB between Caucasians and Japanese.

In Caucasians, CHB occurs in >50% of infant diagnosed with NLE. In Japan, the present review showed a much lower incidence of CHB compared to Caucasians. However, a prospective study from Japan that used follow-up data from mothers showing anti-SS-A/Ro antibody found that about 50% of the infants display CHB[31,32]. This suggests that the diagnosis of NLE may be missed in infants with CHB in Japan.

In Japan, many CHB cases are referred from other fields, such as cardiology and neonatal surgical departments, although many reports about NLE have originated from dermatology departments, with 283 cases of CHB reported in Japan between 1971 and 2008. Conversely, antibody status was known in only 52 of the 283 cases (18%). Anti-SS-A/Ro and/or anti-SS-B/La antibody were positive in 43 patients, representing 15% of the CHB cases, but 83% of cases in which antibody levels were measured. If anti-SS-A/Ro and anti-SS-B/La antibody levels were measured in all patients with CHB, many more patients might have been diagnosed with NLE. These data suggest that cases of NLE showing only CHB are frequently missed in Japan(Table 2).

A pacemaker must be implanted in two-thirds of NLE cases, and the main source of morbidity and mortality in NLE is from CHB. Some reports have shown corticosteroid use during the second trimester in the presence of heart block or myocardial dysfunction may be effective in minimizing the involvement of cardiac systems[33-39]. Many mothers are asymptomatic when the diagnosis of NLE is made, so detailed examinations are not performed, delaying detection and treatment of CHB. Methods for preventing CHB have still not been established, as after the atrioventricular conduction system becomes involved, the effects are irreversible. Checking maternal antibody status is thus central to detecting risk factors for CHB.

In anti-SS-A/Ro antibody-positive pregnant woman, echocardiography should be performed at least every 2 weeks from gestational weeks 16 to 24. Electrocardiography should be performed for all children.

## 5. Conclusions

If anti-SS-A/Ro and anti-SS-B/La antibody levels were measured in patients with CHB, more patients would likely be diagnosed with NLE. Most pregnant women with positive levels of anti-SS-A/Ro and anti-SS-B/La antibodies remain asymptomatic, and the first indications of antibody status are symptoms of NLE in the child. Clinicians such as rheumatologists, dermatologists, cardiologists, neonatologists and obstetricians should thus be acquainted with NLE, and we believe that all pregnant women should be screened for anti-SS-A/Ro and anti-SS-B/La antibodies.

**Figure 1:** Cutaneous NLE. Areas of annular erythema are seen on the cheeks of a 2-month-old Japanese girl. She also presented with liver dysfunction (elevated transaminases). Skin lesions gradually disappeared within 6 months, in parallel with declining serum levels of anti-SS-A antibody.

**Table 1:** Frequency of manifestations in 193 cases of neonatal lupus erythematosus

| Clinical manifestations | No. of infants (%) |
|---|---|
| Cutaneous only | 150 (78%) |
| Cutaneous + congenital heart block | 15 (8%) |
| Congenital heart block only | 28 (15%) |
| Hepatic | 47 (24%) |
| Hematological | 29 (15%) |
| Pancytopenia | 2 |
| Thrombocytopenia | 15 |
| Anemia | 6 |
| Thrombocytopenia + anemia | 1 |
| Hypocomplementemia | 5 |
| Others | 8 (4%) |
| Fever | 2 |
| Hydrocephalia | 4 |
| Gastrointestinal bleeding | 2 |

**Table 2:** Frequency of antibody status in 283 cases of infants with congenital heart block

| Antibody status | No. of infants (%) | | No. of infants (%) |
|---|---|---|---|
| Measured | 52 (18%) | Positive | 43 (15%) |
| | | Negative | 9 (3%) |
| Unknown | 231 (82%) | | |

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