

A 10-year retrospective study of neonatal lupus erythematosus in China

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Summary

Background: Neonatal lupus erythematosus (NLE) is not a common disease. The death rate of complete congenital heart block (CCHB), which is the most severe clinical manifestation, is as high as 20% to 30%, so early recognition of infants at risk is important.

Objectives: To investigate the clinical features and long-term prognosis of NLE.

Methods: Twenty-five cases with NLE were reviewed. The clinical manifestations of patients and their mothers were summarized and analyzed. Autoantibodies were detected, and long-term follow-up was carried out.

Results: There were 25 patients (male:female ratio of 11:14). CCHB was detected in only 3 of the 25 patients (12%). Cutaneous neonatal lupus erythematosus (CNLE) was seen in 22 of the 25 patients (88%). Eight babies were treated with intravenous immunoglobulin (IVIG), five of whom had a prolonged PR interval that reverted to normal sinus rhythm. During the follow-up of the patients, we found only two patients with CCHB without a pacemaker, who both exhibited growth delay. One patient with CCHB without a pacemaker died.

Conclusions: Children with NLE have an excellent outcome when only skin lesions are present. Even the hepatic, hematological and neurological abnormalities are transient, with generally good outcomes. IVIG might have some effectiveness due to enhanced anti-inflammatory activity to treat early diseases that may be

reversible (e.g. prolonged PR interval). The long-term prognosis for patients with NLE is still under investigation, and some infants with NLE may progress to other autoimmune diseases later in childhood. (*Asian Pac J Allergy Immunol* 2016;34:174-8)

Keywords: Neonatal lupus erythematosus, congenital heart block, anti-Ro/SSA or anti-La/SSB antibodies, clinical analysis, prognosis

Abbreviations

CCHB	=	Complete congenital heart block
CNLE	=	Cutaneous neonatal lupus erythematosus
CT	=	Computed tomography
ECG	=	Electrocardiogram
GGT	=	Gamma-glutamyl transferase
IVIG	=	Intravenous immunoglobulin
NLE	=	Neonatal lupus erythematosus
SCLE	=	Subcutaneous lupus erythematosus
SLE	=	Systemic lupus erythematosus
SS	=	Sjögren syndrome

Introduction

Neonatal lupus erythematosus (NLE) is characterized by maternal autoantibodies against the RNA protein complex, i.e. Ro/SSA or La/SSB. It is a passively acquired autoimmune disease in which pathogenic autoantibodies are transplacentally acquired by the fetus.¹⁻⁵ It is characterized by a skin rash (similar to subacute cutaneous lupus erythematosus (SCLE)), hematological and hepatic abnormalities, as well as complete congenital heart block (CCHB) in some cases, a potential fatal complication. The cutaneous, hematological and hepatic abnormalities are transient, clearing by 6 months of age. Cardiac manifestations of neonatal lupus, which comprise complete atrioventricular block or in some cases more extensive injury such as cardiomyopathy, result in fetal death in one fifth of cases and lifelong pacemaker implantation in most surviving infants.⁶ This more extensive injury can occur postnatally, even as late as 10 years of age.⁷ We need to acquire more knowledge on NLE.

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NLE is not a common disease. To our knowledge, most of the reports from China are case reports, and large, retrospective studies have not been published. We retrospectively reviewed the medical charts from the past 10 years (2004-2013) in our department (neonatology department of the Children's Hospital at Zhejiang University School of Medicine, Zhejiang, China); 25 patients with NLE were found. We analyzed the symptoms, prognosis, their mother's condition regarding anti-Ro or anti-La antibodies, and the follow-up of the patients.

Methods

The diagnosis is usually established based on the clinical features and the demonstration of NLE-associated antibodies in the serum of the mother or the affected infant.^{8,9}

The study group consisted of 25 patients with NLE treated in our department from January 1st 2004 to December 31st 2013. No asymptomatic children with isolated laboratory abnormalities were included in this report. We then collected the history of the mothers regarding anti-Ro or anti-La antibodies. This study was approved by the ethical boards, and informed consent was obtained from the parents.

A full history and physical examination was performed. Laboratory testing included a complete blood count with differential white blood cell count, liver function tests (ALT, AST, and gamma-glutamyl transferase [GGT]), as well as the determination of antibodies to SSA/Ro and SSB/La, performed by the clinical immunology laboratory at the Children's Hospital, Zhejiang University School of Medicine using a commercial EUROLINE ANA Profile (D-23560, Lübeck, Seekamp 31, Germany). Reactivity to the 52-kDa SSA/Ro, 60-kDa SSA/Ro, or 48-kDa SSB/La ribonucleoproteins was determined by IBT using SDS-PAGE to separate and then blot proteins onto nitrocellulose; all incubation procedures were performed as described previously.¹⁰ Additionally, we carried out indirect immunofluorescence assays to prevent false positives. For patients, an electrocardiogram (ECG) and echocardiogram were performed routinely. If cutaneous neonatal lupus erythematosus (CNLE) was suspected, the diagnosis was confirmed by a pediatric dermatologist. According to the protocol used in China, patients were followed routinely until the disappearance of autoantibodies from the serum (which usually occurred by 9 months of age). A 24-

hour ECG Holter recording was performed in selected cases.

Twenty-one patients were followed up for 18 months to 12 years. One patient with CCHB died about 1 month after discharge from hospital when he was only one and a half months old. Three of the patients were lost to follow-up. Post discharge, the remaining 21 patients were evaluated at 1 to 2 months until approximately 1 year of age, and every 12 months thereafter.

Results

The study group consisted of 25 patients (14 female patients and 11 male patients). Diagnoses in the mothers were systemic lupus erythematosus (SLE) (5), Sjögren syndrome (SS) (2), undifferentiated connective tissue disease (2), vasculitis (2), rheumatoid arthritis (2), discoid lupus erythematosus (1) and dermatomyositis (1). Ten mothers (40%) were healthy at the time of delivery.

Twenty-two mothers were positive for anti-Ro antibodies; 13 mothers were positive for anti-La antibodies, including 10 mothers who were positive for both anti-La antibodies and anti-Ro antibodies. One mother was positive for anti-U1 ribonucleoprotein autoantibodies. The autoantibodies of the babies were the same as their mothers.

Eight of the 25 patients were born at a gestational age of <36 weeks. The age of onset ranged from 1 day to 27 days (median: 4 days). The clinical presentation is described in Table 1. Furthermore, two cases of sinus bradycardia were detected. Two of the brain CT scans showed symmetrical, diffuse attenuation of the density of cerebral white matter, while the gray matter was normal. Those two patients had no neurological symptoms.

The results of the hematological evaluation, liver function tests and autoantibody assessments are shown in Figure 1.

Treatments: Skin lesions of affected infants were treated with avoidance of sunlight and the use of topical corticosteroids. Eight patients with cardiac symptoms were treated with intravenous immunoglobulin (IVIG) at dose of 1 g/kg for 2 days.

Prognosis: One patient with CCHB died about 1 month after discharge from hospital.

Twenty-one cases were followed up for up to 12 years (median: 3.3 years), and three patients were lost to follow-up. During the follow-up of the patients, we found only two patients with CCHB without a pacemaker who exhibited growth delay. Two patients developed autoimmune diseases: one



Table 1. The clinical presentation of the patients (n=25)

Clinical presentation	Number of patients	Percent (%)
Type of rash		
Annular polycyclic	19	76
Petechiae	3	12
Heart involvement		
Complete congenital heart block	3	12
Prolonged PR interval	5	20
Hematology involvement		
Anemia	2	8
Thrombocytopenia	14	56
Neutropenia	4	16
GI involvement		
Hepatomegaly	2	8
Transaminitis	8	32
Cholestasis	1	4

was diagnosed with juvenile rheumatoid arthritis when she was 5 years old, and one was diagnosed with psoriasis when she was 8 years old.

Discussion

Autoimmune diseases frequently occur in women of childbearing age and affect the developing fetus and the infant. NLE is one of these diseases. The clinical syndrome consists of cardiac abnormalities (most commonly CCHB), cutaneous manifestations, abnormalities of liver function and hematological abnormalities. Cardiac conduction defects detected before or at birth, in the absence of structural abnormalities, are strongly associated with maternal autoantibodies to SSA/Ro and SSB/La ribonucleoproteins, independent of whether the mother has systemic lupus erythematosus or Sjögren's syndrome or is asymptomatic.^{11,12} Buyon et al.⁷ reported on the Research Registry for Neonatal Lupus that was established in 1994; as of October 2008, 416 families had enrolled, in which 449 children had a manifestation of neonatal lupus and maternal sera were shown to contain antibodies to at least SSA/Ro. In total, 260 children (57.9%) had CHB, 36 (8%) had CHB and rash, 139 (31.0%) had a rash only, six had isolated cardiomyopathy in the absence of any conduction defects and eight had isolated hematological or hepatic clinical manifestations alone. Interestingly, in our study,

cutaneous neonatal lupus erythematosus was seen in 22 of 25 patients (88%). Abnormalities of liver function tests were seen in 8 of these patients (32%). Complete congenital heart block, the most serious complication of NLE, was seen in our study in 12% of patients. This percentage is lower than that in previously published studies in America (59%)⁷ and in Japan (50%).¹³ One reason might be that some fetuses with CHB died in utero, or that some of the babies with CHB were unrecognized. Three retrospective studies stated that if a mother is known to have anti-SSA/Ro antibodies and no previous child is affected, the risk of CHB is at or near 2%.^{11,14,15} Another study reported that if the mother has both anti-SSA/Ro and anti-SSB/La antibodies, the risk is slightly higher at 5%. If the mother has antibodies and a prior child with CHB or rash, the risk of CHB in a subsequent pregnancy rises to nearly 20%.⁷ Since China has had a one-child policy since 1980, this may partly explain why the CHB rate in our country is much lower than that in America. Recently, as parents who were the only child in her/his family have been allowed to have two children, there may be an increase in the rate of CHB in babies with NLE.

CCHB is the most severe presentation of patients with NLE, which is permanent and requires a pacemaker in many cases. Because of social and economic reasons, the three patients with CCHB in our study did not have a pacemaker inserted; one died, and two exhibited growth delay. On the one hand, we need to insert pacemakers in babies with CCHB, while on the other hand, it is important to develop new methods to prevent CCHB if possible.

Most of the mothers were positive for anti-Ro or anti-La antibodies or were positive for both. The mothers may have had SLE, SS, or other connective tissue diseases, but some of them were completely healthy at the time of delivery of the child with NLE (about 30% to 40%).^{16, 17} Some of them were not even tested for anti-Ro antibodies or anti-La antibodies until their babies were suspected of NLE. Data from a recently completed prospective open label multicenter study, carried out as part of the PRIDE study (PR Interval and Dexamethasone Evaluation)¹⁵ on dexamethasone use might hold some promise for less advanced blocks and associated cardiomyopathy. The PRIDE study found that a PR interval that exceeds the expected 95% confidence interval of a normal population can be transient, sustained or progressive. Since CHB is most often identified from 18 to 24 weeks gestation

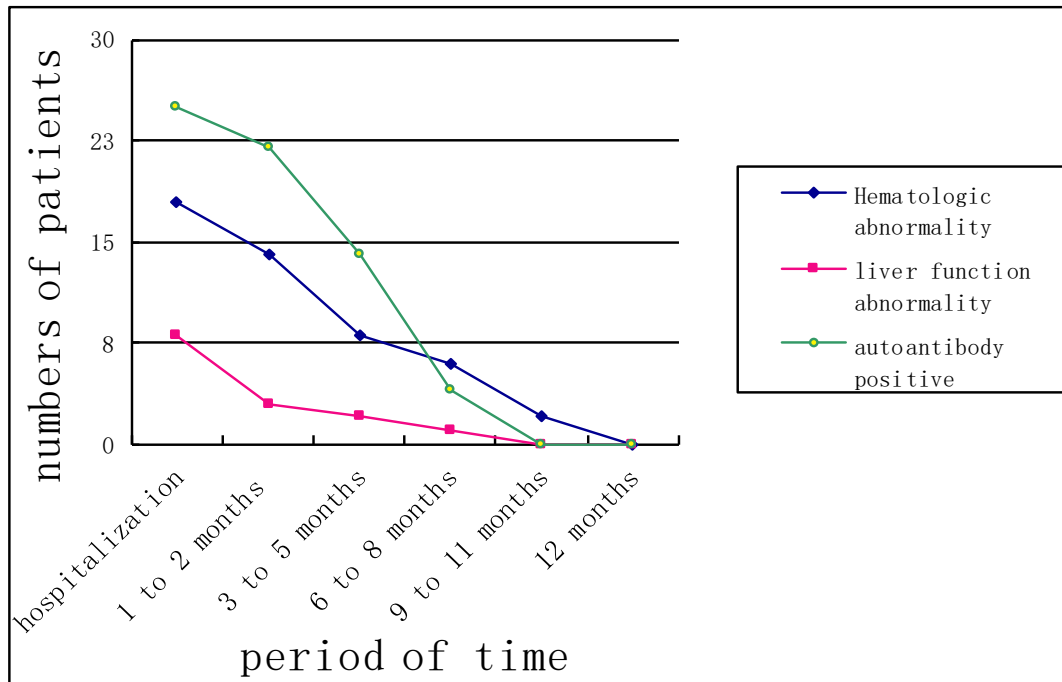


Figure 1. This figure shows the hematologic evaluation, liver function tests, and autoantibodies statements of the 25 patients during hospitalization and 1 to 2 months, 3 to 5 months, 6 to 8 months, 9 to 11 months and 12 months after discharge. It shows that after 9 to 11 months, hematologic evaluation of all the patients were returned to normal range, autoantibodies of all the babies were reverted to negative, after 12 months liver function tests of all the patients were returned to normal range.

and early disease may be reversible,^{6,7} it is important to recognize CHB early and to develop a new prophylactic therapy. In a study comprised of eight pregnancies in mothers with anti-Ro antibodies and a previous child with CHB, treatment with 1 g/kg of IVIG at the 14th and 18th weeks of gestation prevented CHB in seven cases.¹⁸ Factors that may reduce titers of anti-Ro in mothers, such as systemic corticosteroids or plasmapheresis, may reduce the risk of NLE in future offspring or the severity of disease in fetuses with abnormal fetal echocardiograms. So, the identification of fetuses at risk is paramount. It has recently been emphasized that the sialic rich IgG fraction of IVIG confers enhanced anti-inflammatory activity.¹⁹ In our study, five patients had a prolonged PR interval on ECG at birth, after IVIG treatment, all of whom reverted to a normal sinus rhythm. This reinforces the evidence on the effectiveness of IVIG for its enhanced anti-inflammatory activity.

The occurrence of transient sinus bradycardia in two of our cases suggests that not only the atrioventricular node, but also the sinus node could

be involved in NLE. Several reports have shown the same results.^{14,20}

One of the extracutaneous findings that have been reported in patients with NLE, but may not be significant, is neurological abnormalities. In our study, we also found two patients with symmetrical, diffuse attenuation of the density of cerebral white matter, and normal gray matter on brain CT scans. These two patients had no cyanosis, dyspnea, irritability, seizure, hypotonia or decreased physiological reflexes. The follow-up of these two patients showed no abnormalities. Prendiviller reviewed the CT scans of patients with NLE with neurological involvement and observed apparently decreased cerebral white matter and basal ganglia calcification.²¹ Lin et al. reported on one patient with NLE who had transient focal seizures and low density white matter on brain CT scan.²² Jingen reported one patient of NLE with neurological abnormalities without any symptoms;²³ the brain CT scan showed the same results as we found in our study. The prognosis is good for NLE patients with neurological involvement.

Conclusions

Children with NLE have excellent outcomes when only skin lesions are present. Even hepatic, hematological and neurological abnormalities are transient, and have a good prognosis. IVIG might be effective for its enhanced anti-inflammatory activity to treat patients with early disease that may be reversible (i.e. a prolonged PR interval). The long-term prognosis for children with NLE is still under investigation and infants with NLE may need long-term follow-up.

Limitations

First, because NLE is a rare disease, the incidence of NLE is low, and the number of the patients in this study is small. A larger sample size is needed to demonstrate significance.

Conflict of interest

None declared.

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