Neonatal lupus erythematosus (NLE) is a model of passively acquired autoimmune disease in which pathogenic autoantibodies are transplacentally acquired by the fetus. The mothers may have systemic lupus erythematosus (SLE), Sjögren syndrome (SS), or other connective tissue diseases, or may be completely healthy at the time of delivery of the child with NLE. The laboratory hallmark of the disease is the presence of autoantibodies directed against the Ro particle. The most important and severe clinical manifestation of NLE is complete congenital heart block (CCHB), which carries a significant morbidity and mortality. Other cardiac features include congenital malformations and less severe conduction abnormalities. Hepatic involvement, usually cholestatic, and hematologic abnormalities such as anemia and thrombocytopenia have also been reported. A skin rash can be apparent at birth or during the first months of life and is usually transient, disappearing by age 6 to 9 months; however, some children will develop telangectasias.

Despite numerous reports on NLE, the true incidence of each individual manifestation is not known because most data were from case reports or retrospective studies. It has been stated that skin rash occurs in as many as half of the patients and liver disease in about 10%. However, to our knowledge, large, prospective studies to determine the true incidence of each individual manifestation have not been published. Moreover, there is little prospective data on the true incidence of CCHB in infants born to mothers with anti-Ro or anti-La antibodies or both.

**INCIDENCE AND SPECTRUM OF NEONATAL LUPUS ERYTHEMATOSUS:**
**A PROSPECTIVE STUDY OF INFANTS BORN TO MOTHERS WITH ANTI-RO AUTOANTIBODIES**

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**Objective** Neonatal lupus erythematosus (NLE) is characterized by complete congenital heart block (CCHB), cutaneous rash, and laboratory abnormalities in infants born to mothers with autoantibodies directed against SSA/Ro, SSB/La, or both. We carried out a prospective study to determine the incidence of individual NLE features.

**Study design** The study was performed in two centers: Toronto, Canada, and Milano, Italy. Mothers had been referred for the presence of anti-SSA/Ro autoantibodies, regardless of their diagnosis. All the children were seen at least once within the first 6 months of life for clinical evaluation and laboratory testing. The study group consisted of 128 infants born from 124 pregnancies in 112 women with anti-Ro antibodies with or without anti-La antibodies.

**Results** There were two cases of CCHB for an overall percentage of 1.6%. Twenty-one children (16%) developed cutaneous NLE. Laboratory testing showed hematologic abnormalities in 27% of the babies and elevation of liver enzymes in 26%.

**Conclusions** Mothers with autoimmune diseases and anti-Ro antibodies are at risk of delivering a child with NLE but at a low risk of delivering a child with CCHB. Infants born to mothers with anti-Ro or anti-La antibodies should be monitored for other features of NLE in addition to CCHB. (J Pediatr 2003;142:678-83)
The primary aim of the current study was to determine the incidence of each individual feature of NLE in infants born to prospectively followed pregnant women with anti-Ro with or without anti-La antibodies. The second objective was to determine whether the presence or absence of a maternal autoimmune disease influenced the development of NLE in the offspring.

MATERIALS AND METHODS

The study group consisted of 128 infants born in two different centers (Toronto, Canada, and Milano, Italy) to mothers who were positive for anti-Ro with or without anti-La antibodies at the time of pregnancy. All mothers were contacted during pregnancy. Both hospitals are tertiary referral centers for NLE, and the study group was composed of patients born during the periods 1987 to 2000 (Toronto) and 1996 to 2000 (Milano). Mothers were referred, and their children subsequently enrolled in this study, on the basis of a diagnosis of connective tissue disease, a previous child with a history of NLE, or the presence of autoantibodies in an otherwise healthy woman. All mothers were positive for anti-Ro. This study was approved by the ethics boards at both centers, and informed consent was obtained from the parents.

All children were seen by one of the investigators at least once within 6 months of birth. A full history and physical examination was performed. Laboratory testing at the visit included a complete blood count with differential white blood cell count, liver function tests (ALT, AST, and gamma-glutamyl transferase [GGT]), and an autoantibody profile. Sera were analyzed for anti-Ro and anti-La autoantibodies by enzyme-linked immunosassays using affinity-purified proteins (in Toronto, affinity-purified Ro and La proteins were a gift from Immunovision, Springfield, Kan). For patients enrolled in Toronto, an electrocardiogram (ECG) and echocardiogram were performed when clinically indicated, whereas all infants seen in Milano had an ECG routinely performed. Mothers were asked at enrollment to report whether the child developed any rash between visits. All suspicious rashes were seen, and if cutaneous neonatal lupus erythematosus (CNLE) was suspected, the diagnosis was confirmed by a pediatric dermatologist. According to the protocol used in Milano, children were followed routinely until the disappearance of autoantibodies from the serum (which usually occurred by 9 months of age). At each visit a standard ECG was obtained in addition to the laboratory tests (Milano only). A 24-hour ECG Holter recording was performed in selected cases.

The study group consisted of 128 infants (66 male infants and 62 female infants) born from 124 pregnancies (four twin pregnancies) in 112 different women. One hundred five infants (102 pregnancies in 91 different mothers) were born in Toronto, and 23 infants (22 pregnancies in 21 different mothers) in Milano. The majority of these women (95 mothers) had been referred because they had been previously diagnosed with an autoimmune disorder or because they were known to have anti-Ro with or without anti-La antibodies. Diagnoses in these mothers were SLE (68), SS (seven), undifferentiated connective tissue disease (five), vasculitis (two), rheumatoid arthritis (one), discoid lupus erythematosus (one), Raynaud phenomenon (one), and dermatomyositis (one). Nine mothers were healthy at the time of delivery (they had been referred for fetal echocardiogram and were enrolled in the study on the basis of their autoantibody profile). Seventeen women were referred (all in Toronto) because of a previous child with a major manifestation of NLE: 13 with CCHB and four with CNLE. Six of these mothers had SLE, three SS, one isolated Raynaud phenomenon, and one mixed connective tissue disease, and the other six were healthy before and during the referral pregnancy and at the time of delivery of all of their children.

The mean age of the mothers at the time of delivery was 31 years (range, 18–40 years). All of the mothers were positive for anti-Ro antibodies; 58 mothers also had anti-La antibodies, and 12 had anti-U1 ribonucleoprotein autoantibodies. In all cases the autoantibodies were also detected in the newborn’s sera.

RESULTS

There were 128 live births and 124 pregnancies. Only 10 of the 128 babies (7.8%) were born at a gestational age of <36 weeks. The Figure shows the incidence of each of the individual manifestations of NLE.

Complete congenital heart block was detected in only two of the 128 births (1.6%). Both of these infants with CCHB were born to mothers who had previously delivered a child with NLE. Therefore there was a 10.5% (2/19) incidence of CCHB in children born to mothers who had previously delivered a child with NLE and a 0% incidence of CCHB in children of mothers with a known autoimmune disease but without a previously affected child. However, a prolonged QT interval was detected in nine of 22 infants (41%) in whom an ECG was performed. A further two cases of sinus bradycardia were detected. All of these 11 cases were seen in Milano, where ECGs were routinely performed, and all mothers of these babies had a known autoimmune disease.

Cutaneous neonatal lupus erythematosus was seen in 21 of the 128 children (16%). We did not find any statistically significant difference in the percentage of children with CNLE born to women with a known autoimmune disease or carrying anti-Ro or anti-La antibodies (16/109, 15%) compared with offspring born to mothers who had a previous baby with NLE (5/19, 26%) (P = NS, \( \chi^2 \)). In the whole cohort, the presence of anti-La in addition to anti-Ro seemed to increase the risk for CNLE, because CNLE was more frequently present in the children positive for anti-Ro and anti-La than in those carrying only anti-Ro (\( P < .01 \)).

Laboratory Abnormalities

Infants (n = 124) had hematologic evaluations performed on at least one occasion. The initial testing was performed in all infants during the first 5 months of life: 20 infants in the neonatal period, 21 during the first month of life, 47 during the second month, 21 during the third month, eight during the fourth month, and seven during the fifth month. Twenty-seven percent of these babies (33/124) had at least one of the following conditions at the time of initial testing: anemia, thrombocytopenia, and neutropenia. All hematologic results were compared with the age-matched normal
values. The most common abnormality was neutropenia (<1000 neutrophils/mm³), seen in 25 of 107 tested (23%). Despite the neutropenia there were no cases of sepsis. More than one hematologic abnormality was seen in two of 124 of the infants (1.6%).

In Milano, children were evaluated at birth, after 1 to 2 months, and every 2 to 3 months thereafter until approximately 1 year of age. Abnormal hematologic studies were most frequently seen at age 1 to 2 months rather than at birth, because 50% (11/22) of the infants tested at 1 to 2 months had at least one of anemia, thrombocytopenia, or neutropenia, compared with abnormal values in 13% (3/23) of the patients studied at birth. Hematologic abnormalities were seen in 39% (7/18) of the infants tested at age 3 to 5 months, 36% (4/11) of the infants tested at age 6 to 9 months, and 25% (2/8) of the infants tested after 9 months of life. These latter two infants were not subsequently retested because they continued to grow normally and did not display any physical abnormality.

Liver function tests were obtained at least once in 120 infants, and abnormalities were seen in 31 of these infants (26%). As with the hematologic evaluation, the initial liver function tests were obtained within 5 months of delivery. At least one serum transaminase was abnormal in 19% of the cases. There were similar percentages of infants with elevation of ALT (9/120, 7.5%) and AST (7/121, 5.8%) (P = NS, χ²). In addition, evidence of biliary obstruction (elevation of GGT) was seen in five of the 45 infants (11%) tested on at least one occasion. As with hematologic evaluations, serial liver functions were obtained only in the infants from Milano. Unlike the results for hematologic studies, the most frequent time for detection of an abnormal liver function test was the perinatal period, because abnormalities were seen in 16/19 (84%) of neonates. However, abnormalities continued to be apparent throughout the first year of life, present at 1 to 2 months of age in 15 of 21 patients (71%), at 3 to 5 months in 11 of 17 (65%), at 6 to 9 months in eight of 10 (80%), and at 10 to 12 months in five of six (83%). Laboratory abnormalities were usually mild, and none of the infants displayed any clinical symptoms at any time during the follow-up period; therefore, children were discharged from the clinic at 1 year of age. Abnormalities were generally isolated to either elevated transaminases or GGT, and only 5% of patients had both abnormalities.

The prevalence of laboratory abnormalities was not statistically significantly different in children born to mothers with an autoimmune disease compared with children born to healthy women (P > .05 for both measurements, χ²). Maternal disease was not statistically significantly associated with any laboratory feature of NLE in the offspring (P = NS, χ²) (Table).

**DISCUSSION**

Autoimmune diseases frequently occur in women during their childbearing age and may affect the developing fetus and the infant. NLE is a disease of the developing fetus and neonate which is associated with maternal anti-Ro, anti-La, and, less frequently, anti-U₁RNP antibodies. The clinical syndrome consists of cardiac abnormalities, most commonly CCHB; cutaneous manifestations; abnormalities of liver function; and hematologic abnormalities. NLE has
been reported to occur in approximately 1% to 2% of children born to women with SLE, with rates as high as 15% to 20% in children born to women with SLE and anti-Ro antibodies. Many centers, including our own, have studied cardiac outcomes in children born to women with anti-Ro and anti-La antibodies, but no large study had previously been undertaken to study all manifestations of NLE in a large population of women with anti-Ro or anti-La antibodies regardless of maternal health. In this study we found that 52% of newborns born to mothers with a known autoimmune disease and anti-Ro antibodies, or to mothers who had previously delivered a child with NLE, had at least one manifestation of NLE. We could also confirm that the presence of anti-Ro (with or without anti-La) autoantibodies, rather than the type of maternal autoimmune disease, is a risk factor for the development of NLE. Interestingly, and in agreement with previous studies, children with CCHB were born to mothers who had previously delivered a child with NLE. Complete congenital heart block, the most serious complication of NLE, was seen in our study in 1.6% of the prospectively followed pregnancies of women positive for anti-Ro antibodies. Many centers, including our own, have studied cardiac outcomes in children born to women with anti-Ro than in children of mothers with anti-Ro and anti-La antibodies, without those antibodies, we found a prolonged QT interval in a high percentage of our infants. The findings of QT abnormalities should be confirmed in larger series, but a prolonged QT interval is a risk factor for sudden infant death.

The incidence of noncardiac features of NLE has rarely been studied. Existing data on the incidence of these features have been usually derived from retrospective studies, which may result in an underestimation of the occurrence of CNLE, anemia, thrombocytopenia, or abnormal liver function tests in the absence of clinical signs or symptoms. A high incidence of hematologic abnormalities was found in our series. The hematologic abnormalities were asymptomatic and mostly resolved by 1 year of age. Anti-Ro and anti-La antibodies are likely the cause of the cytopenias seen in NLE, because the neutrophil membrane contains a Ro cross-reactive 64-kd protein that has been implicated in the neutropenia seen in patients with SLE and in one of our NLE cases, and because the Ro antigen is present in red blood cells as well.

In our series no child had clinical evidence of liver dysfunction (hepatomegaly, jaundice), but ~25% of the infants showed asymptomatic elevation of liver function tests, which is higher than the previous reported incidence of ~10%. Unlike

### Table. Incidence of the clinical features of neonatal lupus in infants born to mothers with and without autoimmune diseases

<table>
<thead>
<tr>
<th>Maternal diagnosis</th>
<th>Number of cases (mothers/children)</th>
<th>CCHB (%)</th>
<th>Rash (%)</th>
<th>Hepatic abnormalities (%)</th>
<th>Hematologic abnormalities (%)</th>
<th>Well (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>74/84</td>
<td>0</td>
<td>13 (15)</td>
<td>16 (19)</td>
<td>22 (26)</td>
<td>43 (51)</td>
</tr>
<tr>
<td>SS</td>
<td>10/11</td>
<td>1 (9)</td>
<td>4 (36)</td>
<td>4 (36)</td>
<td>4 (36)</td>
<td>5 (45)</td>
</tr>
<tr>
<td>UCTD</td>
<td>5/5</td>
<td>0</td>
<td>0</td>
<td>3 (60)</td>
<td>0</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Other</td>
<td>8/10</td>
<td>0</td>
<td>2 (20)</td>
<td>5 (50)</td>
<td>3 (30)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Healthy</td>
<td>15/18</td>
<td>1 (5.5)</td>
<td>2 (11)</td>
<td>3 (16.6)</td>
<td>4 (22)</td>
<td>12 (66.6)</td>
</tr>
</tbody>
</table>

*Results are shown as the number of cases, with the percentage of cases in parentheses. UCTD, Undifferentiated connective tissue disease.
in previous studies, including the study from the NLE Research Registry, we screened all patients for these abnormalities, not just patients referred for the presence of skin or cardiac disease or liver failure. We suggest that our incidence better approximates the true incidence of liver function test abnormalities and that the reported figures reflect the incidence of coincident hepatic disease in children with CCHB or CNLE.

The skin lesions of NLE are usually annular inflammatory lesions resembling those seen in subacute cutaneous lupus erythematosus or annular erythema and are usually most prominent on the face. We found that 16% of all children born to mothers with anti-Ro antibodies with or without anti–La antibodies had the skin rash characteristic of NLE, a higher figure than the incidence of conduction abnormalities in our series. To our knowledge this is the first prospective study examining the incidence of CNLE in a large cohort of babies born to women with anti-Ro antibodies. The nationwide US registry for NLE has enrolled 57 infants with CNLE diagnosed in a period of 17 years, and a single-center report has described 18 babies seen in a period of 20 years by three experienced dermatologists. However, these latter reports were retrospective, and it is not clear how many women with anti-Ro antibodies had children during the time of the study. It is of note that many of the children reported in the US registry were initially diagnosed as having a fungal infection or eczema; Weston et al reported that in the vast majority of their cases of CNLE, the correct diagnosis was not suspected until evaluation by a dermatologist. We think that our 16% incidence of skin rash likely reflects the true incidence of CNLE in infants born to mothers with anti–Ro antibodies because our study was prospective, a physical examination was performed on all babies within 6 months of age, and mothers were specifically instructed to call if any rash was seen on the infant.

In conclusion, we have shown that infants born to mothers with anti–Ro with or without anti–La antibodies more frequently demonstrated both clinical and laboratory features of NLE than previously reported. In addition, our incidence of CCHB in infants born to anti–Ro antibody–positive mothers was lower than that in earlier retrospective or smaller studies but similar to that in a recent large, prospective study. We suggest that NLE should be considered as a potential cause of idiopathic thrombocytopenia, anemia, neutropenia, and abnormal liver function tests detected before age 1 year, regardless of maternal health. In addition, we suggest that infants born to mothers with anti–Ro or anti–La antibodies or both should be monitored for features of NLE in addition to CCHB.

We acknowledge Prof Pierluigi Meroni for referral of several mothers in this study, performance of laboratory testing, and continuous support and discussions.

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50 Years Ago in The Journal of Pediatrics

CHEST DEVELOPMENT IN EARLY CHILDHOOD

Kornfeld W. J Pediatr 1953;142:715-20

Fifty years ago, Dr. Kornfeld noted that the neonatal chest shape normally changes from an upright cone to an inverted one in the older child. This anthropometric evolution he documented by two measurements of chest circumference—one just above the nipples and another at the xiphoid. He suggested that alterations in the relationship between these two might be a predictor of developmental abnormalities. In the mid-1960s I became interested in ways by which one can quantitate the degree of a child’s chronic obstructive pulmonary disease, especially in cystic fibrosis. With the help of two Tulane medical students (S. E. Acker and E. S. Golladay) we began to measure, with obstetric calipers and metal tape measure, the thoracic depth, thoracic width, and circumference at the nipple line of every child on each visit to the chest clinic. (Later, depth and width measurements were greatly facilitated by the development by Warwick and Hansen of special calipers with a built-in metric scale.) It soon became clear that circumference was not a good measure of obstructive lung disease, because, as obstruction worsened, the depth of the chest increased at a greater rate than either its width or circumference. We developed a graphing system that allowed one to plot depth as a function of width and thereby obtain this so-called thoracic index without further calculation. Differences in terms of standard deviation units from the expected values for both depth and width as a function of height could be immediately determined by means of a checkerboard background on the graph. The graphs were printed in color and distributed without charge by Mead Johnson Laboratories.

On at least one occasion, such serial measurements were most helpful. Dr. Judith Harris and I began to treat selected patients with cystic fibrosis and associated growth failure with an anabolic steroid (Dianabol). In many children, we noted with pleasure healthy increases in weight and height but no significant changes in pulmonary function. What led us to abandoning the use of the drug was an alarming increase in chest depth, indicating progression of pulmonary obstruction.

Today I fear that thoracic anthropometry is passé. Several current pediatric pulmonary texts allude to it briefly, some suggesting chest circumference as being simpler than the dimensions obtained by calipers, and one altogether omitting discussion of such measurements.

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