Neonatal Lupus Erythematosus

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Introduction

• Neonatal lupus erythematosus (NLE) refers to a clinical spectrum of cutaneous, cardiac, and systemic abnormalities observed in newborn infants whose mothers have autoantibodies against Ro/SSA, La/SSB, and, less commonly, U1-ribonucleoprotein (U1-RNP).
Introduction

• The condition was first described in 1954 by McCUistion and Schoch who reported a case of transient lupus skin lesion in an infant with an ANA-positive mother.
Introduction

• The most common presentation is a nonscarring, nonatrophy skin lesion which resemble subacute cutaneous lupus erythematosus.

• The infants may have no skin lesions at birth but develop them during the first weeks of life.
Introduction

• Cardiac, hematological, hepatobiliary, central nervous, and pulmonary systems may also be involved.

• NLE is associated with transplacental passage of autoantibodies such as anti-RoSSA and anti-La/SSB.
Introduction

- The condition is usually benign and self-limited but sometimes may be associated with serious sequelae.
Pathophysiology

• A number of studies have suggested that NLE is caused by the transplacental passage of maternal autoantibodies.
Pathophysiology

• These autoantibodies may cause damage to the developing tissue and increase the risk of bearing infants with NLE.

• Approximately 98% of affected infants have maternal transfer of autoantibodies against Ro/SSA, La/SSB, and, less commonly, U1-RNP.

• However, only 1-2% of mothers with these autoantibodies have neonates with NLE, regardless of whether the mothers are symptomatic or not.
Pathophysiology

- The 52-kD Ro/SSA (Ro52) ribonucleoprotein is an antigenic target strongly linked with the autoimmune response in mothers whose children have NLE, congenital heart block, and other conduction abnormalities.
Pathophysiology

- Anti-Ro52/SSA autoantibodies antagonize the serotonin-induced L-type calcium channel activation on human fetal atrial cells and trigger an inflammatory response, leading ultimately to fibrosis and scarring of the atrioventricular node, sinus node, and His bundle.
Pathophysiology

• The antibodies associated with heart block and with cutaneous disease are believed to be different; antibodies against the 52/60-kD Ro/SSA and 48-kD La/SSB ribonucleoproteins are associated with heart block, whereas antibodies against the 50-kD La/SSB ribonucleoprotein are associated with cutaneous disease.
Pathophysiology

• The spectrum of cutaneous disease in U1RNP antibody-positive infants is similar to Ro/SSA antibody-positive infants with NLE.

• Complete heart block was not a feature of U1RNP antibody-positive NLE.

• HLA typing studies show a more diverse immunogenetic pattern in U1RNP antibody-positive mothers of infants with NLE compared with Ro/SSA antibody-positive mothers.
Pathophysicsology

- It has been shown that the amount of maternal antibodies, rather than their presence, is associated with fetal tissue injury.

- However, only some neonates exposed to these antibodies develop complications.
Cardiac Involvement

• The risk of NLE or congenital heart block developing in a woman who tests positive for Ro/SSA who has never had a child with NLE or congenital heart block is less than 1%.

• Many seropositive mothers with anti-Ro/SSA and anti-La/SSB antibodies give birth to infants who do not show signs and symptoms of NLE.

• However, in those who have had an infant with NLE, the risk of cardiac and/ or skin disease for a future pregnancy is high.
Cardiac Involvement

• The incidence of congenital heart block is 15–30% in infants with NLE.

• Heart block usually develops in utero between the 18th and 24th weeks of pregnancy.

• Infants born to mothers with hypothyroidism due to thyroid autoantibodies and antiRo/SSA positivity are at nine times higher risk of developing congenital complete heart block than infants born to mothers with only anti-Ro/SSA positivity.
• Approximately 40–60% of mothers are asymptomatic when the infants are diagnosed to have NLE.

• The remaining mothers may have SLE, Sjogren syndrome, rheumatoid arthritis, or undifferentiated autoimmune disorder.

• Mothers with primary Sjogren syndrome or undifferentiated autoimmune syndrome have a greater risk of delivering an infant with congenital complete heart block than those with SLE.

• There is no association with paternal autoimmune diseases.
Clinical Manifestation

• The most common clinical manifestations of NLE are, in decreasing order of frequency, dermatologic, cardiac, and hepatic abnormalities.

• Some infants may also have hematologic, neurologic, or splenic abnormalities.
Clinical Manifestation

• Cutaneous lesions may be present at birth but often appear within the first few weeks of life.

• Annular erythematous or polycystic plaques with or without fine scales characterize NLE and appear predominately on the scalp, neck, or face (typically periorbital in distribution), but similar plaques may appear on the trunk or extremities.

• The dermatitis resembles the rash of subacute cutaneous lupus erythematosus rather than the malar rash of SLE.
**Clinical Manifestation**

- Periorbital erythema, referred to as “raccoon eye” or “owl eye,” is a very common characteristic.

- At times, the lesions may be urticarial, desquamative, ulcerative, or crusted.

- Bullous lesions may be seen with a particular predilection for the soles of the feet.
Clinical Manifestation

• The cardiac manifestations include conduction abnormalities (first-, second-, and third-degree heart block) and cardiomyopathy.

• Third-degree heart block, once established, is usually irreversible.

• Congenital heart block may present as bradycardia noted in utero or during physical examination at birth.

• Conduction disturbances may also present as irregular heartbeat and prolongation of the QT interval.
Clinical Manifestation

• Congenital heart block may be associated with endocardial fibroelastosis and cardiomyopathy.

• In some cases, myocarditis and pericarditis can develop which may lead to bradycardia.

• Heart failure is a well-recognized complication during the neonatal period.
Clinical Manifestation

• The clinical pictures of hepatobiliary involvement may take the forms of elevation of liver enzymes (such as aspartate aminotransferase and alanine aminotransferase) and/or conjugated hyperbilirubinemia occurring a few weeks or months after birth and resolving thereafter.

• Some infants may have mild hepatomegaly and, less commonly, splenomegaly.

• The hepatomegaly and splenomegaly are usually transient.
• Cholestatic hepatitis and hepatic failure may also occur.
Clinical Manifestation

• Hematologic disturbances (e.g., hemolytic anemia, thrombocytopenia, and neutropenia) may occur in the first 2 weeks of life.

• Infants with hematological involvement are usually asymptomatic.
• Autoantibodies, mainly antiRo, bind directly to the neutrophil and cause neutropenia.

• Thrombocytopenia may manifest as petechiae. Hematologic symptoms usually appear at around the second week of life and disappear by the end of the second month.

• Lymphopenia is a relatively common finding in adults with SLE but is not a characteristic hematologic abnormality of NLE.
Diagnosis

• 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.

• NLE can mimic many conditions.

• Differential diagnosis of NLE includes seborrheic dermatitis, atopic dermatitis, neonatal acne, tinea corporis, psoriasis, granuloma annulare, erythema multiforme, Langerhans cell histiocytosis, congenital rubella, congenital syphilis, Bloom syndrome, and Rothmund-Thomson syndrome.
Diagnosis

• NLE is associated with the anti-Ro/SSA antibody in more than 90% of patients
• Occasionally, patients only have anti-La/SSB or anti-U1RNP antibodies.
• Screening of infants with NLE for the presence of these antibodies is strongly recommended.
• Many asymptomatic mothers have positive putative antibodies during pregnancy
Diagnosis

• As such, these mothers of patients suspected of having neonatal lupus erythematosus should be screened for antinuclear, anti-doublestranded DNA, anti-Ro/SSA, anti-La/SSB, and anti-U1-RNP antibodies, irrespective of their symptoms or clinical status.

• As anti-Ro/SSA antibodies can be detected in one in 200 pregnant women, the risk for an anti-Ro/SSA-positive woman to have an infant with NLE is relatively low.
Diagnosis

• On the other hand, high anti-Ro/SSA levels correlate with the risk of cardiac complications.
• Serial prenatal ultrasonography/electrocardiography should therefore be performed on pregnant women with high anti-Ro titers (≥50 U/mL).
• Prenatal ultrasonography may help identify NLE that affects the heart.
Diagnosis

- Echocardiography may reveal various types of structural deformities in the heart; combined electrocardiography and 24-hour Holter monitoring may reveal various cardiac conduction disorders or different types of heart blocks.
Diagnosis

- Skin biopsy is useful in patients with NLE when the diagnosis is in doubt.

- Histologic examination shows interface dermatitis, keratinocyte damage, moderate hyperkeratosis, follicular plugging, and vacuolar degeneration in the basal cell layer.
Diagnosis

• Inflammatory infiltrate may be intense with bulla formation histologically.
• An immunofluorescent examination reveals a granular deposition of immunoglobulin G (IgG) at the dermoepidermal junction; IgM and C3 deposition may also be evident.
• Skin biopsy is not pathognomonic.
Management

• Neonates with NLE should be managed at a tertiary care center.
• Multidisciplinary team involvement may also be indicated.
• Patients with NLE with cardiac involvement require regular monitoring to assess cardiac function and the need for a pacemaker.
Management

• A pacemaker is often necessary for those who are unable to compensate for a slow heart rate.
• Serial echocardiography to monitor for a prolonged PR interval should also be arranged.
• If the cardiac involvement is severe, activity may have to be restricted in the young child.
Management

- Sunscreens may be useful in the treatment of cutaneous lupus erythematosus, but a neonate is less likely to be exposed to sunlight excessively.
- Nevertheless, solar exposure should be avoided if possible.
Management

• Parents should be advised to apply sunscreen well before solar exposure and to use a sunscreen with a high SPF that provides a broad-spectrum (UVA) coverage which is water resistant.

• Behavior modification to include solar avoidance should be encouraged.
Management

• Protective clothing is highly desirable. Strategies aimed at preventing disease before irrevocable scarring ensues are a high priority. Skin lesions of NLE can be treated with mild topical corticosteroids.

• Antimalarial agents have potential toxicity and a slow onset of action that their use in the treatment of this transient condition is probably not indicated.
Management

• Laser therapy may be considered for residual telangiectasia.

• Systemic corticosteroids and immuno-suppressive agents are generally not indicated in the treatment of NLE.
Management

• Children with NLE need continued followup, especially before adolescence and if the mother herself has an autoimmune disease.

• Although the child may not be at increased risk of developing SLE, the development of some form of autoimmune disease in early childhood may be of concern.

• Infants with severe hepatic and hematological involvement may require treatment with systemic corticosteroids, intravenous immunoglobulin, and/or immunosuppressive agents.
Management

• occur later in life as a result of the failure of the pacemaker.

• However, many children with congenital heart block may be relatively asymptomatic until adolescence, when they begin to exercise.

• At that time, they may develop syncope and require a pacemaker implantation
Management

• The recurrence rate of congenital heart block is low, about 15%, but this is nearly three times higher than the risk for congenital heart block in a primigravida with the putative antibodies.

• Prospective clinical trials on use of antenatal fluorinated steroids in women with anti-SSA/Ro and/or antiSSB/La antibodies and fetuses with heart block identified in utero are required before definitive recommendations can be made.

• A number of anecdotal cases support the use of dexamethasone for treatment of hydrops and possibly incomplete block.
Treatment

• Most patients with NLE affecting liver or blood have transient disease that spontaneously resolves within 4–6 months.

• In some cases, cholestatic hepatitis and liver failure may occur which is associated with a poor prognosis.
Treatment

• Although the fetal disease is called neonatal lupus erythematosus, this is considered a misnomer since only about 25% of mothers actually fulfill criteria for the diagnosis of SLE.

• Furthermore, asymptomatic mothers do not invariably become ill.
Treatment

• Mothers of infants with NLE, particularly infants with congenital heart block, have a 2-fold to 3-fold increased risk of having an affected infant in a subsequent pregnancy.

• On the other hand, the risk for an unselected anti-Ro/SSA-positive woman has been estimated at 1-2%.
Treatment

• A prospective controlled study of pregnancy outcome in 100 women with autoimmune diseases and anti-Ro/SSA antibodies showed that the prevalence of congenital heart block in newborns of prospectively followed up women already known to be anti-Ro/SSA positive and with known connective tissue disorders was 2%.
Treatment

• In mothers with anti-Ro/SSA and/or anti-La/SSB antibodies and infants with congenital heart block, the risk of recurrence in subsequent offspring is 17–25%.

• Therefore, carefully monitoring of subsequent pregnancies with serial ultrasonography and echocardiography, particularly at 18–24 weeks’ gestation, is essential
Treatment

• Intravenous immunoglobulin merits evaluation as a potential prophylactic approach in mothers who have previously had an affected child.
• However, two studies failed to demonstrate benefit in outcome from intravenous immunoglobulin.
• On the other hand, the use of hydroxychloroquine for patients with SLE has been associated with a lower rate of NLE during pregnancy.
Treatment

• Mothers with SLE should be treated with drugs that are effective and safe for the fetus.
• Such an approach may diminish or reduce the prevalence of complete heart block associated with NLE.
• Tincani et al. recently reported increased occurrence of learning disabilities in children born to mothers with SLE.
Treatment

• Corticosteroids and some immunosuppressive drugs can be used in pregnancy to control maternal disease.
• Some data suggest that prolonged fetal exposure to dexamethasone may impair cerebral development.
• On the other hand, Tincani et al. followed 6 children (age range, 14–65 months), born to patients treated with dexamethasone because of congenital heart block.
Treatment

• These children were found to have a normal intelligence quotient.

• However, the authors remarked that information about long-term outcome of children exposed to immunosuppressive drugs “in utero” are still lacking, and more efforts are needed in this research area.