Neonatal Lupus and Related Autoimmune Disorders of Infants

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Author Disclosure
Drs Frankovich, Sandborg, Barnes, Hintz, and Chakravarty have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives

After completing this article, readers should be able to:

1. Describe the broad spectrum of clinical manifestations associated with neonatal lupus.
2. Explain pathogenic mechanisms of maternal autoantibody–associated neonatal disease.
3. Review appropriate screening measures for congenital heart block.
4. Discuss infant and maternal evaluation for suspected neonatal lupus.
5. Delineate long-term implications for affected infants and subsequent pregnancies.

Abstract

Neonatal lupus syndromes are caused by maternal antibodies targeting proteins displayed on apoptotic blebs. Mothers frequently are healthy and unaware of their autoantibody status. Manifestations in infants include rashes, cytopenias, hepatobiliary disease, heart block, and rarely, cardiomyopathies. Cerebral dysmaturation, ventriculomegaly, and lenticulostriate vasculopathy are recently described manifestations. Rhizomelic chondrodysplasia punctata, pneumonitis, nephritis, and multiorgan failure are rare. Coexisting antithyroid and antiphospholipid antibodies may complicate the presentation. Symptoms typically disappear with the clearance of maternal antibodies from the neonatal circulation, except in cases where the disease is extensive or involves vulnerable tissues. Early diagnosis, close monitoring, and appropriate intervention with immunosuppressive treatment may subvert organ-threatening disease in select cases.

Introduction

The neonatal lupus syndromes (NLSs) present with protean features, posing diagnostic dilemmas for the neonatologist. Contributing to the puzzle, 50% of affected infants have healthy mothers. Transplacental passage of antinuclear and ribonuclear autoantibodies target fetal and neonatal tissues for immune destruction. The most common manifestations are rashes, cytopenias, and hepatobiliary disease. Heart block and cardiomyopathies are rare but cause significant morbidity and mortality. Coexisting antithyroid and antiphospholipid antibodies also can lead to neonatal complications. Recent studies suggest that central nervous system (CNS) injury may be another part of NLSs.

Asymptomatic mothers can have autoantibodies and give birth to infants who have lupus rashes, heart block, and abnormal brain imaging studies. Maternal seropositivity often is discovered after an affected infant is born. Many women who have autoantibodies have not been diagnosed with a rheumatic disease. They may have subclinical disease or no disease at all and, thus, are unaware of their antibody status.

Half of infants who have NLS are born to mothers who have diagnosed rheumatic conditions: Sjögren's disease, systemic lupus erythematous (SLE), mixed connective tissue disease, leukocytoclastic vasculitis, various forms of arthritis,

Abbreviations

ANA:	antinuclear antibody
APL:	antiphospholipid
CHB:	congenital heart block
CNS:	central nervous system
Ig:	immunoglobulin
IVIg:	intravenous immunoglobulin
NLS:	neonatal lupus syndrome
RNP:	ribonuclear protein
SLE:	systemic lupus erythematosus
SSA/Ro:	anti-Sjögren's syndrome A antibody (also known as anti-Ro antibody)
SSB/La:	anti-Sjögren's syndrome B antibody (also known as anti-La antibody)

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immune-mediated thrombocytopenia, thyroiditis, autoimmune hepatitis, and undifferentiated autoimmune syndromes. In our experience, disease activity during pregnancy is a risk factor for neonatal complications. For example, gestational-onset maternal SLE confers a high risk for neonatal morbidity, with 75% of affected infants being admitted to the neonatal intensive care unit. (1)

Although most clinical manifestations of NLS resolve with disappearance of maternal autoantibodies from the neonatal circulation, long-term sequelae can cause significant morbidity. Infants benefit from comprehensive evaluation and early intervention. In addition, studies suggest that infants who have NLS are at risk of developing autoimmune diseases in childhood. Consultation with pediatric rheumatology is helpful for complete evaluation, monitoring, management, and long-term follow-up of affected infants.

NLS is a disease resulting from maternal antibodies. This is in contrast to primary infantile SLE, which results from the infant's intrinsic deregulated immune system, frequently involves the kidneys, and requires aggressive immunosuppression. NLS is the focus of this review because it is far more common than primary infantile SLE.

Fetal Antigens: Target of Maternally Derived Autoimmune Pathology

Autoantibodies are present in approximately 10% of women in childbearing years, often fluctuate in quantity and type over time, and can affect the developing fetus. Many of these autoantibodies target cells undergoing apoptosis. During physiologic apoptosis, previously sheltered nuclear antigens and phospholipids are translocated to the cell surface and are displayed on immunogenic surface blebs. If clearance of apoptotic debris is impaired or the burden of apoptotic debris overwhelms clearance mechanisms, the immune system forms antibodies to these nuclear antigens and phospholipids. Antinuclear antibodies (ANAs) include anti-Sjögren's syndrome A (SSA/Ro), anti-Sjögren's syndrome B (SSB/La), ribonuclear protein (RNP), and DNA antibodies and frequently coexist with antiphospholipid (APL) antibodies. Autoantibodies often are benign or they can induce inflammatory damage to bystander tissue, including blood vessels and organs, leading to clinical autoimmune diseases.

Immunoglobulin G (IgG) antibodies cross the placental barrier starting in the second trimester, reach maternal concentrations by 30 weeks' gestation, and exceed maternal concentrations by term. (2) When autoantibodies are passed to the fetus, they target fetal/neonatal antigens, leading to clinical NLS, with damage to the neonatal skin, bone marrow, liver, heart, and possibly the blood vessels and CNS tissues.

Animal models have shown that maternal autoantibodies mediate fetal autoimmune disease. The fetuses of pregnant mice given intraperitoneal injections of human autoantibodies (SSA/Ro, SSB/La) had human IgG-apoptotic cell complexes in the skin, liver, heart and newly forming bone. (3) Phagocytosis of opsonized apoptotic cells is proinflammatory and is the presumed link between maternal autoantibodies and immune-mediated damage to fetal tissues. (4)

Neonatal Manifestations of Maternal Autoimmunity (Table)

Cutaneous Manifestations and Residual Skin Abnormalities

The classic NLS rash is characterized by round or elliptical erythematous, papulosquamous lesions with central clearing, annular erythema, and a fine scale (Fig. 1). Lesions typically involve the face and scalp but also are found on the neck, trunk, extremities, and intertriginous areas. The lupus malar rash is rare in infants who have NLS; the periorbital rash (resembling raccoon's eyes) is common.

The classic NLS rash is associated with the 52-kD SSA/Ro, 60-kD SSA/Ro, 48-kD SSB/La, and U1RNP autoantibodies. It becomes apparent during the first 3 postnatal months, frequently is induced or exacerbated by ultraviolet light (sunlight or phototherapy), and persists for a mean of 4 months. In isolated cutaneous NLS, affected neonates appear clinically well. The rash spontaneously resolves by 6 to 8 months of age as maternal autoantibodies disappear from the infant's circulation.

Residual skin abnormalities occur in 10% to 25% of infants and include telangiectasias, dyspigmentation, pitting, scarring, and skin atrophy. Some clinicians use topical corticosteroids, but efficacy has not been established. Avoidance of sun exposure can prevent or minimize the rash and residual skin abnormalities.

A blueberry muffin rash should prompt evaluation for both congenital infections and NLS. In the case of NLS, extramedullary dermal erythropoiesis is due to severe intrauterine anemia mediated by maternal autoantibodies; affected infants also have hepatosplenomegaly and thrombocytopenia (Fig. 2).

Hematologic Cytopenias

Immune suppression of the bone marrow by maternal autoantibodies is the proposed cause of cytopenias in NLS, but peripheral destruction of blood components

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Table. Neonatal Lupus Syndrome

Clinical Manifestations (Relative Frequency + to ++++)		Treatment/Monitoring	Long-term Prognosis
Skin	1) Round, elliptical, erythematous lesions. Periorbital, malar, scalp, neck, trunk, extremities, intertriginous areas (++++) 2) Blueberry muffin rash (+)	1) Avoid sun/ultraviolet light exposure; consider topical corticosteroids 2) Evaluate for anemia	1) 10% to 25% have residual atrophy, telangiectasias, and dyspigmentation 2) Resolves
Hematologic	1) Anemia (+++) 2) Hemolytic anemia (+) 3) Thrombocytopenia (+++) 4) Neutropenia (+) 5) Bone marrow failure (+) 6) Disseminated intravascular coagulation (+) 7) Thromboses related to APL antibodies (+)	Mild: No treatment Moderate/severe or refractory anemia or thrombocytopenia: First-line: IVIg 1 g/kg for 1 to 2 days Second-line: Corticosteroids 1 to 2 mg/kg for 5+ days⟶slow wean Thromboses: Consult hematology	Few patients need blood product transfusions to bridge recovery time if symptomatic anemia/ thrombocytopenia
Vascular	1) CNS vasculopathy (++) 2) Placental vasculopathy, infarction, and thrombosis associated with APL antibodies (+++)	1) Unknown 2) Variable	1) See CNS vasculopathy section. 2) Placental abnormalities may result in prematurity and IUGR
Cardiac	1) Bradyarrhythmias due to heart block and other cardiac conduction abnormalities, including PR interval elongation (+) 2) Myocarditis, endocarditis, ventricular endomyocardial fibroelastosis (+) 3) CHF, ± pleural/pericardial effusions (+)	1) Close monitoring, pacemaker for life-threatening conduction abnormalities 2) Corticosteroids if active carditis 3) Heart failure management	20% mortality if complete CHB; incomplete block and other conduction abnormalities may progress Myo/endocardial involvement confers a poor prognosis
Liver	1) Direct hyperbilirubinemia, mild transaminitis (0 to 3 wk) (+++) 2) Mild transaminitis (2 to 3 mo of age) (+++) 3) Severe hepatic dysfunction (perinatal period) (+)	Corticosteroids if severe or persistent transaminitis	First two categories have excellent prognosis; third category is similar to neonatal iron storage disease
Renal and pulmonary	1) Glomerulonephritis, nephrotic syndrome (+) 2) Pneumonitis, pulmonary capillaritis, pulmonary hemorrhage (+)	Aggressive immunosuppression	Primary infantile SLE is likely factor
Prematurity and lung immaturity	Risk of prematurity (++) is increased if the mother has: 1) Active rheumatic disease 2) APL antibodies 3) Thyroid disease	Depends on clinical manifestations	Variable
CNS	1) Cerebral dysmaturation (++) 2) Cerebral dysgenesis (+) 3) Dysmaturity and dysgenesis of structures downstream of lenticulostriate vessels (+) 4) Seizures (+)	If abnormal tone, poor feeding, other neurologic symptoms: Obtain magnetic resonance imaging and head ultrasonography ± Doppler Electroencephalography if seizures suspected	Mostly unknown Increased risk of learning disorders if mother has SLE and APL antibodies Infants who have lenticulostriate vasculopathy may have an increased risk of tics, attention deficit, hyperactivity, obsessions/ compulsions
Multiorgan dysfunction	Anemia ± thrombocytopenia, liver dysfunction, respiratory failure, prematurity, ± thromboses, ± thyroid dysfunction, ± cardiac conduction abnormalities, ± CNS abnormalities	Consider corticosteroids and/or IVIg; consult rheumatology	Variable
Musculoskeletal	Rhizomelia, punctate calcifications in epiphyses (+)	Genetics consultation	
Ophthalmologic	Congenital nystagmus, optic nerve hypoplasia (+)	Direct association with maternal autoimmunity not established to date	

APL=antiphospholipid, CHB=congenital heart block, CHF=congenital heart failure, CNS=central nervous system, IUGR=intrauterine growth restriction, IVIg-intravenous immunoglobulin, SLE=systemic lupus erythematosus

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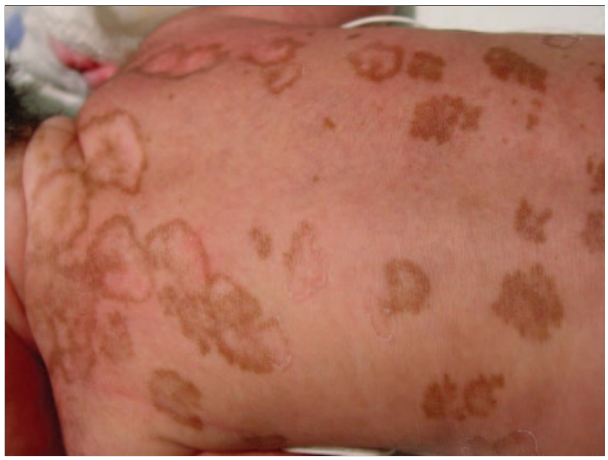

Figure 1. Neonatal lupus rash illustrating elliptical papulosquamous lesions with central clearing. Extensive dyspigmentation is apparent. Courtesy of Judith V. Williams, MD, Director of Dermatology, Children's Specialty Group, Norfolk, Va.

also occurs. Thrombocytopenia and anemia are the most common hematologic manifestations, can occur separately or together, typically worsen over the first days after birth, and resolve after disappearance of maternal autoantibodies. Other signs of bone marrow involvement include teardrop cells and basophilic stippling. Neutropenia and aplastic anemia are rare.

SSA/Ro and SSB/La antibodies are associated with neonatal cytopenias. The extent to which other maternal autoantibodies mediate these hematologic abnormalities is unknown. Antiplatelet antibodies have been described but are uncommon in NLS.

Hemolytic anemia is a rare manifestation of NLS. Immune thrombocytopenic purpura with microangiopathic hemolytic anemia and disseminated intravascular coagulation have been reported in an infant who had NLS. (5)

In cases of fetal thrombocytopenia, postnatal management typically involves observation when platelet counts are greater than 20.0×10^3/mcL (20.0×10^9/L) and there are no signs of bleeding. Anemia is usually mild and self-resolves. Intravenous immunoglobulin (IVIg) and corticosteroids are instituted in cases of persistent, severe hematologic manifestations. The authors recommend an initial trial of IVIg 1 g/kg for 1 or 2 days. If the response is insufficient or not sustained, corticosteroids at 1 to 2 mg/kg may be initiated for 5 days or until an adequate response is achieved, followed by a slow taper. Single-donor, cytomegalovirus-negative irradiated blood products should be administered to control bleeding or to treat symptomatic anemia. However, blood product transfusions typically do not result in sustained counts when autoantibodies are present. Most infants do not need treatment and have spontaneous resolution of hematologic abnormalities with disappearance of maternal antibodies.

Hematologic abnormalities frequently coexist with other NLS manifestations. Therefore, affected infants require evaluation for skin, liver, cardiac, bone, and CNS abnormalities.

APL Antibodies, Placental Vasculopathy, and Neonatal Thromboses

APL antibodies are associated with increased risk for arterial and venous thromboses and are found in 5% of healthy women and 30% of women who have SLE. APL antibodies are associated with placental vasculopathy, infarction, and thrombosis, which can lead to recurrent pregnancy loss, preeclampsia, placental insufficiency, fetal growth restriction, and preterm birth.

Transplacentally acquired APL antibodies may be risk factors for neonatal thrombosis, especially in the setting of sepsis, indwelling catheters, or other situations where

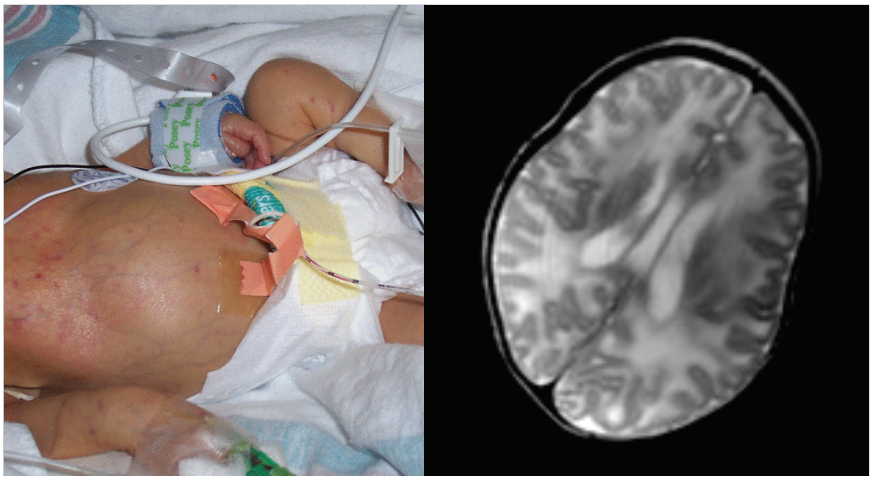

Figure 2. (Left) Blueberry muffin rash an in infant who has NLS. Anemia, thrombocytopenia, liver dysfunction, and congenital hypothyroidism complicated the presentation. (Right) Brain magnetic resonance imaging shows prominent lateral ventricles, cavum septum pellucidum, and marked T2 hyperintensities throughout the cerebral white matter (dysmaturity, hypomyelination).

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vessel injury predisposes to thromboses. Case reports reviewed by Cimaz and Descloux (6) describe APL antibody-associated neonatal thromboses involving cerebral blood vessels, the renal vein, mesenteric vessels, and the aorta. This review also described a case of Blalock-Taussig shunt thrombosis and neonatal catastrophic APL syndrome involving multiple small-vessel thromboses. It is not clear whether these thrombotic events are coincidental or a true manifestation of APL antibodies. Most infants born to mothers who have APL antibodies do not develop thrombotic complications.

Hepatobiliary Disease

Liver disease occurs in 9% to 25% of infants who have NLS. (7)(8) As with all NLS manifestations, hepatic disease may be isolated or occur within a wider spectrum of the NLS. The primary manifestations are transaminitis, cholestasis, and hepatosplenomegaly.

The two most common presentations of NLS liver disease are: 1) direct hyperbilirubinemia with mild or no transaminitis occurring in the first few weeks after birth and 2) mild transaminitis occurring at 2 to 3 months of age. (8) Severe perinatal hepatic dysfunction, often with the phenotype of neonatal iron storage disease, portends a poor prognosis. (8)

Biopsy is reserved for infants who have severe liver dysfunction or persistent moderate dysfunction. Histopathology ranges in severity, but typically shows mild bile duct obstruction, portal fibrosis, and occasional giant cell transformation similar to idiopathic neonatal giant cell hepatitis. (9)

For severe or persistent moderate transaminitis, corticosteroids initiated at 1 to 2 mg/kg for 5 days or until an adequate response is achieved, followed by a slow wean, have been used successfully at our institution. Transaminases should be monitored weekly during the corticosteroid wean, and worsening transaminitis should prompt escalation of corticosteroids. Most infants have spontaneous resolution of liver abnormalities by 3 to 6 months after clearance of maternal autoantibodies. Deaths from hepatic failure have been reported; judicious use of immunosuppression should be considered to prevent liver damage.

Cardiac Conduction Abnormalities and Other Cardiovascular Manifestations

Antibody-mediated injury to fetal and neonatal cardiac conduction tissue has been confirmed in both in vivo and in vitro studies, (10)(11)(12) and NLS accounts for 85% of all cases of congenital complete heart block (CHB). (13)

The incidence of heart block in infants born to mothers who have anti-Ro/SSA or anti-La/SSB antibodies is 1% to 2%, and the recurrence rate in subsequent pregnancies is 16% to 18%. (7)(14)(15) Antibodies alone are insufficient to induce conduction system fibrosis; other factors are essential in the inflammatory cascade. Studies support a progression of events: cardiocyte apoptosis, translocation of SSA/Ro and SSB/La antigens to the cardiocyte surface, binding of maternal autoantibodies, macrophage recruitment, secretion of profibrosing factors, and ultimately, fibrosis of the cardiac conduction system. (6)(7)(8)(9)(10)(11)(12)(16)(17)(18)(19)

Complete CHB causes significant morbidity and mortality, with 65% of surviving neonates ultimately requiring pacemakers and a cumulative probability of death at 3 years of 20%. (14) Incomplete heart block can progress to higher degrees of block years after the postnatal period. (19) Additional electrocardiographic abnormalities have been reported, including transient sinus bradycardia, QT interval prolongations, and Wolff-Parkinson-White syndrome. (19)(20)

Myocarditis and ventricular endocardial fibroelastosis (16)(21)(22) can occur with NLS. Pathologic studies reveal inflammatory cell infiltrates and deposition of Ig, complement, and fibrin in the myocardium. Postnatal development of cardiomyopathy has a poor prognosis and occurs in approximately 10% of infants who have NLS-associated CHB. (21) In addition to cardiomyopathies, aortic stenosis with Ig deposition (17), ventriculoseptal defects, and patent ductus arteriosus have been reported.

Screening for SSA/Ro and SSB/La should be considered for women who have rheumatic complaints, histories of autoimmune condition, or strong family histories of autoimmunity. Moreover, pregnancy-related hormones can trigger autoimmune disease. Seropositive mothers are at risk for having children who have CHB and require monitoring of the fetal mechanical PR interval by echocardiography weekly from 16 to 26 weeks' gestation. In addition, some institutions recommend biweekly monitoring from 26 to 32 weeks' gestation. Most cases of CHB are detected before 30 weeks' gestation, with a peak incidence between 20 and 24 weeks. (14)

After delivery, infant electrocardiography should be obtained. When bradyarrhythmias or other arrhythmias are detected perinatally, infants should be monitored closely for progression of conduction abnormalities and cardiomyopathies.

Currently, only anecdotal and retrospective data guide therapy of in utero cardiac complications. Fluori-

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nated corticosteroids and sympathomimetics are used in mothers of affected fetuses for treatment of in utero effusions, hydrops fetalis, and other complications of advanced heart block. (18)(23)(24)(25)(26) Efficacy of corticosteroids in preventing progression of heart block is controversial and may not outweigh the risks of adverse effects. Plasmapheresis and intrauterine placement of a fetal pacemaker also have been attempted. (27)(28) Limited success is reported with intrapartum IVIg to prevent and treat CHB, but the safety profile maybe better than that of corticosteroids. (29)(30)(31)

Two National Institutes of Health-sponsored prospective trials currently are underway to evaluate the safety and efficacy of maternal oral dexamethasone in treating newly identified CHB and prophylactic IVIg in mothers who have a previous child afflicted with NLS heart block or rash (*http://clinicaltrials.gov/ct2/show/NCT00007358?term=neonatal+lupus&rank=2* and *http://clinicaltrials.gov/ct2/show/NCT00460928?term=neonatal+lupus&rank=3*).

Pulmonary and Renal Manifestations

Pneumonitis, pulmonary capillaritis, glomerulonephritis, and nephrotic syndrome are rare manifestations of NLS and may be suggestive of infantile primary SLE. (32)(33) One infant who had CHB and a pacemaker born to a mother who had SSA/Ro and SSB/La antibodies presented with tachypnea, cough, and hypoxemia at age 3 months. (34) The chest radiograph showed diffuse bilateral interstitial infiltrates, and the lung biopsy confirmed the presence of necrotizing capillaritis and alveolar hemorrhage. Another infant presented at 1 month of age with pulmonary hemorrhage and glomerulonephritis due to infantile SLE, confirmed serologically and histologically. (35) Both patients did well after aggressive immunosuppressive therapy.

Endocrine Manifestations

Autoimmune thyroid diseases frequently coexist in women who have ANA, SSA/Ro, and SSB/La antibodies. Thyroid disease in women who have SLE and Sjögren syndrome approaches a prevalence of 14% to 20%. (36) When assessing sick infants who have NLS, evaluation for thyroid dysfunction and maternally derived thyroid antibodies, both blocking and stimulating Igs, should be considered. Transplacental passage of antithyroid antibodies is associated with thyroid disease of neonates, both hypo- and hyperthyroidism, and indirect hyperbilirubinemia. (37)

Signs and symptoms of neonatal hypothyroidism include constipation, hypotonia, hypokinesis, hypothermia, lethargy, hoarse cry, feeding difficulty, prolonged jaundice, dry skin, umbilical hernia, macroglossia, and large fontanelles. However, most affected infants lack clinical signs and symptoms. They can present with tachypnea, tachycardia, hypertension, arrhythmias, congestive heart failure, goiter with tracheal obstruction, exophthalmos (stare), hyperkinesis, diaphoresis, flushing, frequent vomiting, diarrhea, hypoglycemia, and poor weight gain.

Infants who have transplacentally acquired thyroid antibodies can have a delayed presentation of thyroid dysfunction. Therefore, periodic monitoring for signs and symptoms or thyroid-stimulating hormone screening is recommended.

Women who have hypothyroidism and SSA/Ro antibodies have a ninefold increased risk for delivering a child who has CHB compared with women who have only SSA/Ro antibodies. (38) It is unknown whether the increase in risk of cardiac conduction problems is caused by low thyroid hormone concentrations or a direct effect of thyroid antibodies.

Adrenal dysfunction has been reported in one infant who had transplacentally acquired antiphospholipid antibodies and bilateral massive adrenal hemorrhage. (39) Adrenal insufficiency should be suspected in an infant who exhibits hypotension and eosinophilia.

Musculoskeletal Manifestations and Maternal Lupus Serology

There have been 10 case reports of rhizomelic chondrodysplasia punctata in babies born to mothers who had SLE antibodies. (40) These infants had midfacial hypoplasia, shortening of the proximal limbs, and punctate calcifications of the epiphyses in at least one of the following regions: humerus, femur, tibia, tarsal bones, heels, phalanges, and spine (cervical, thoracic, lumbar, sacral, coccygeal regions, and anterior spinal ligament). Two were stillborn and eight were preterm (range of 24 to 36 weeks, median of 33.5 weeks). Only three of the infants had an NLS rash, but four had CNS manifestations (developmental delay in three and static encephalopathy in one). Of these 10 cases, none had cataracts or defects in peroxisomal metabolism, which is typical of the genetic forms of chondrodysplasia punctata. (40) All 10 mothers had SLE, but three were diagnosed postnatally. It is unclear whether teratogen exposure was a factor in these cases.

Mouse studies support an autoimmune mechanism in lupus-related cases of rhizomelic chondrodysplasia punctata. SSA/Ro and SSB/La antibodies are common in

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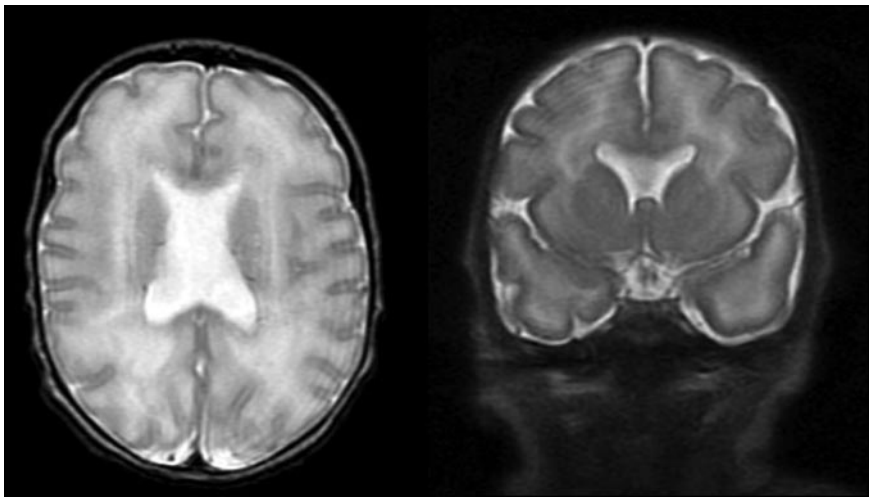

Figure 3. Axial (left) and coronal (right) brain magnetic resonance imaging shows slightly prominent lateral ventricles and absent septum pellucidum with marked T2 hyperintensities throughout the cerebral white matter (dysmaturity, hypomyelination) and a coarse gyral pattern (cortical immaturity).

women who have SLE and frequently predate the development of clinical SLE. As previously mentioned, IgG–apoptotic cell complexes were found in bones of all fetuses born to mice injected with SSA/Ro and SSB/La antibodies. Importantly, these immune complexes were found in the zones of newly forming bone. (3) Immune complex-mediated inflammation at growth plates may be a cause of epiphyseal dysplasia and subsequent rhizomelia, midfacial hypoplasia, and other bone/cartilage anomalies found in infants born to mothers who have SLE. As with all lupus-related complications, the degree of dysplasia can range from mild (subclinical) to severe and depends both on infant factors and maternal autoantibody subtypes and titers.

Spastic paresis, truncal hypotonia, and delayed walking have been reported but are likely related to CNS injury rather than muscular involvement.

Clinical Neurologic Disease and Maternal Autoantibodies

Most infants who have NLS do not exhibit overt neurologic symptoms at the time of birth, although a spectrum of CNS abnormalities has been observed: cerebral dysmaturation, cortical dysgenesis, ventriculomegaly, and dysgenesis of structures supplied by the lenticulostriate vasculature (Figs. 2 and 3). Seizures, strabismus, opsoclonus, truncal hypotonia, spastic paresis, myelopathies, cerebral hemorrhages, static encephalopathies, and developmental delay also have been observed in association with maternal autoantibodies. Taken together, these clinical observations suggest a potential association between maternal autoimmunity and neonatal CNS injury, which must be validated in larger epidemiologic studies.

Radiologic evidence of white matter disease was reported in 6 of 11 consecutive term infants presenting to a dermatology clinic with a neonatal lupus rash. (41) The reduced attenuation of white matter seen on the six computed tomography scans indicates increased water content commonly seen with cerebral edema and hypomyelination. The white matter resembled that of preterm infants, although every infant was term. (41) All of the mothers had SSA or SSB antibodies, although only one had received a diagnosis of a rheumatic disease. (41)

Lenticulostriate vasculopathy is a commonly reported complication of NLS. (41)(42)(43)(44)(45) In one study, echogenic lenticulostriate vessels on ultrasonography or basal ganglia calcifications were present in 5 of 11 term infants who had NLS rash. (41) Basal ganglia calcifications are believed to be due to "mineralizing lenticulostriate vasculopathy," which has been reported in autopsy cases but is not a universal finding in infants who have lenticulostriate vasculopathy. Histologic involvement of a pericallosal artery also was demonstrated in an infant in whom ultrasonography only showed gangliothalamic vasculopathy. (45)

Subependymal cysts, hemorrhages, and ventriculomegaly also are reported commonly. (41)(42)(45)(46)(47)(48) Subependymal cysts in the caudothalamic groove (typical site of germinal matrix hemorrhages) have been reported in term infants who had NLS but no perinatal complications. (41) Recently, a large study found an association between neonatal intraventricular hemorrhage and lenticulostriate vasculopathy that was statistically significant after controlling for confounders. (49) The prevalence of hydrocephalus and macrocephaly also is increased in infants born to mothers who have anti-SSA/Ro antibodies (8% versus 0.05% in the general population). (46)

In addition to the previously mentioned CNS abnormalities, the following imaging findings were seen in infants who had NLS at the author's institution: thalamostriatal malformations (globular basal ganglia), ab-

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sent septum pellucidum, prominent cavum septum pellucidum, optic chiasm and optic nerve hypoplasia, and cortical dysgenesis (polymicrogyria and coarse gyral patterns). If cerebral dysgenesis is included as a possible complication of germinal matrix disruption, all of these imaging findings may be the result of inflammation and impaired blood flow from lenticulostriate vasculopathy and choroid plexopathy.

It is not known whether the aforementioned cases are true associations or confounded associations because preterm birth, preeclampsia, and hypertension complicate some of these pregnancies.

Biologic plausibility for the association between neonatal CNS injury and maternal autoantibodies is supported by the known connection between these autoantibodies (SSA, SSB, other ANAs, APL, thyroid antibodies) and adult human CNS disease, including CNS vasculitis, periventricular and diffuse white matter lesions, chorea, seizures, and cognitive dysfunction. Such diseases are well known in the setting of SLE, Sjögren syndrome, and APL syndrome. Additionally, antithyroid antibodies are associated with small-vessel CNS vasculitis and corticosteroid-responsive encephalopathy and seizures.

Animal studies show that APL antibodies mediate neurologic dysfunction when injected into the intrathecal space of mice (50)(51)(52) and cross-react with epitopes associated with myelin, brain ependyma, or choroid epithelium in felines. (53) Anti-SSA/Ro antibodies have been shown to modulate inward calcium currents (54) and may have a role in seizures if these antibodies cross a disrupted blood-brain barrier. Anti-dsDNA antibody (an ANA subtype) injected into mice cross-react with NR2A epitope of the glutamate/NMDA receptor, leading to excitotoxic injury to the mouse brain. (55)(56)

Given the clinical association of these autoantibodies and CNS disease in adults, animal studies of autoantibody-mediated neurologic damage, and case reports/series of CNS disease in neonates, it is reasonable to consider a maternal autoimmune evaluation in the context of unexplained neonatal CNS disease, especially in cases of diffuse hypomyelination, ventriculomegaly, lenticulostriate vasculopathies, and associated dysgenesis and dysmaturation of the cerebrum or diencephalon. In cases of neonatal seizures, it is important to consider evaluation of the infant's cerebrospinal fluid for SSA, SSB, and dsDNA antibodies if these antibodies are present in the mother.

There is a paucity of studies evaluating long-term neuropsychiatric consequences in infants who have NLS. One study suggests an increased rate of learning disabilities in children born to women who have SLE and concurrent APL antibodies. (57) Infants who have idiopathic lenticulostriate vasculopathies may have an increased risk of developing attention deficits, hyperactivity, obsession/compulsion, and tic disorders. (58) Infants who had late lenticulostriate vasculopathies (detected after 10 days of age) were likely to have muscle tone abnormalities at 6 months of age. (59) Further studies are needed to determine accurate risk estimates in infants who have NLS.

Multiorgan Involvement in NLS

In most cases, affected neonates present with an isolated manifestation of NLS, although multiorgan dysfunction can occur. The most common multiorgan presentation of NLS is a sick preterm infant who has anemia, thrombocytopenia, liver dysfunction, and respiratory failure. In addition to the standard evaluation for congenital infection, a timely evaluation for NLS, including electrocardiography and maternal autoantibody profiles, may facilitate diagnosis. In addition, maternal thyroid and APL antibodies may be measured and a careful neurologic examination undertaken with consideration of head ultrasonography, magnetic resonance imaging, and electroencephalography in symptomatic infants.

Infant/Maternal Autoantibody Evaluation: When, Why, and How

Evaluation for maternal autoantibodies should be undertaken if any of the previously described stigmata are present without a clear cause, irrespective of the severity of individual manifestations. A suggested algorithm for evaluation is shown in Figure 4 . Because neonatal manifestations are caused by the passive transfer of maternal autoantibodies, the initial screening can be conducted using maternal serum or cord blood to conserve the infant's blood. A complete evaluation for congenital infection should be pursued simultaneously because many features of congenital infections mimic NLS and require prompt antibiotic therapy.

The initial maternal antibody screen should include an ANA, SSA, and SSB. These tests are readily available, easy to obtain on the mother, do not require infant blood loss, and may yield important information on how to treat the affected infant as well as future pregnancies in the mother. If the mother tests positive for an autoantibody, strongly consider consultation with pediatric rheumatology to facilitate further characterization of the immune profile, close evaluation of the infant for

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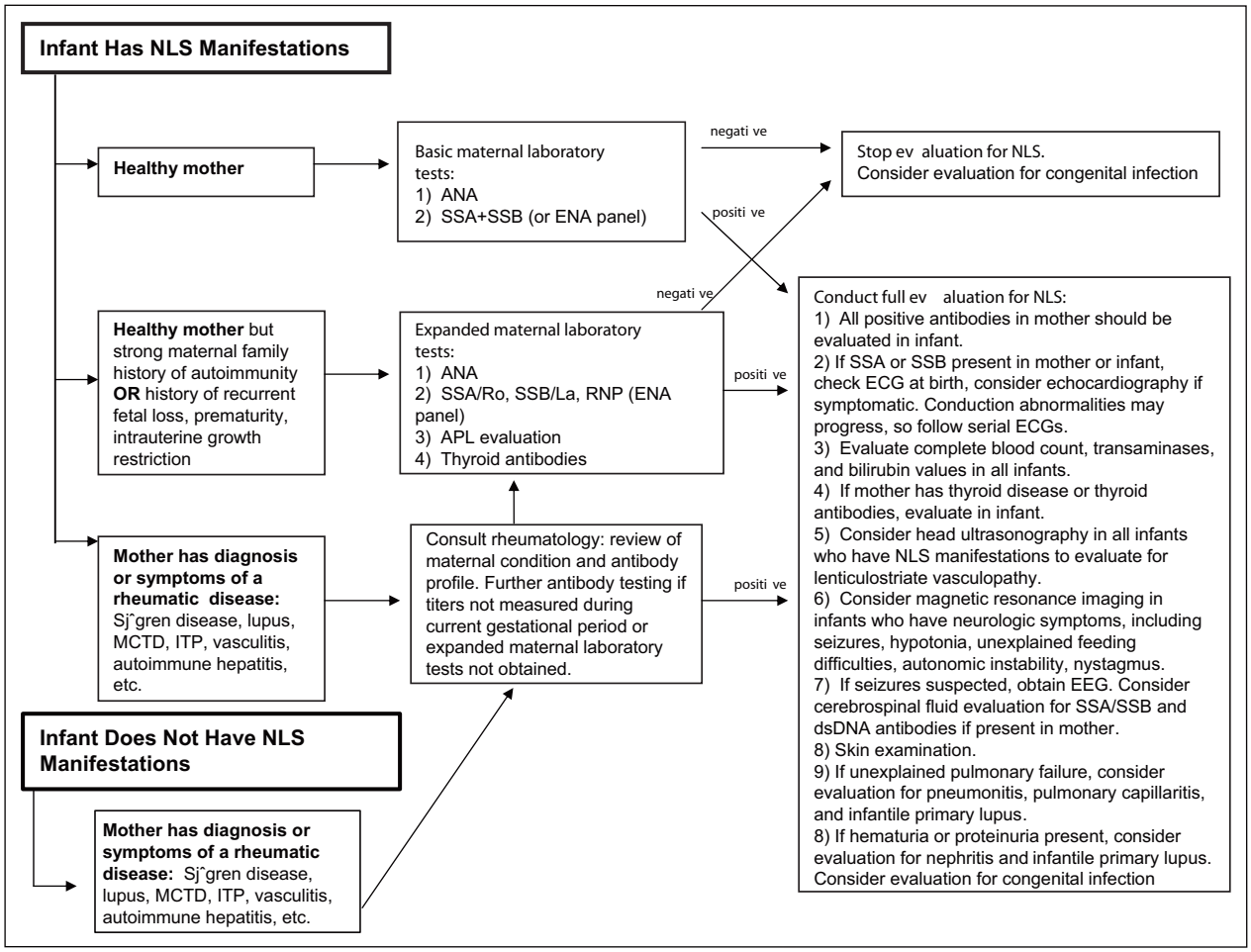

Figure 4. Infant and maternal evaluation of NLS. ANA=antinuclear antibodies, APL=antiphospholipid antibodies, ECG=electrocardiography, EEG=electroencephalography, ITP=immune thrombocytopenic purpura, MCTD=mixed connective tissue disease, RNP=ribonuclear protein

NLS stigmata, and appropriate referral of the mother to an adult rheumatologist.

If the infant or mother is ill or the ANA subtiters are positive, maternal evaluation for antithyroid antibodies and APL antibodies may be pursued because these frequently coexist, are passed transplacentally to the fetus, and can cause fetal and neonatal complications. For any autoantibodies found in the mother, corresponding autoantibodies should be measured and tracked in the infant. In addition, appropriate clinical and laboratory measures should be evaluated (eg, electrocardiography, echocardiography, head ultrasonography, liver function tests, complete blood count) and monitored until disappearance of autoantibodies and correction of other clinical parameters. For infants who have neurologic symptoms, including hypotonia, poor feeding, and bradyarrhythmias, brain magnetic resonance imaging should be considered strongly.

The value of identifying infants who have maternal autoantibodies is enormous. Critically ill infants may benefit from immune modulation and close monitoring of related complications, including CHB, liver disease, hematologic manifestations, thyroid dysfunction, thromboses, and CNS complications. Identification of an infant who has NLS is an important trigger for monitoring succeeding pregnancies in the mother using fetal echocardiography and antibody titers. If a mother ultimately is diagnosed with a rheumatic disease, optimal treatment of the underlying disease can improve the outcomes of future pregnancies. Finally, infants who have NLS are at a higher risk of developing other autoimmune diseases in childhood, regardless of a benign

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presentation of NLS. (54) Proper identification of NLS and parent education may aid in early recognition of future autoimmune illnesses in the child.

NLS Classification and Research Registry

Currently, no formal classification criteria for NLS exists. The Research Registry for Neonatal Lupus was established by the National Institute for Arthritis, Musculoskeletal and Skin Diseases. For the purposes of this Registry, the following two criteria must be met: 1) heart block or classic NLS rash, and 2) maternal autoantibodies targeting defined SSA/Ro, SSB/La, and RNP subtypes. (14) This Registry serves as a rich resource for the study of infants/mothers satisfying the previously noted criteria, but it does not capture the sundry manifestations and large spectrum of autoantibodies that may be causing fetal/neonatal injury, including CNS manifestations.

Conclusion

NLS is caused by maternal autoantibodies targeting proteins displayed on apoptotic blebs. Apoptosis is a normal part of fetal development and organ morphogenesis, including the cardiac conduction system and the CNS. Although extensive research has targeted maternal autoantibody-mediated damage to the developing fetal cardiac conduction system, few investigators have evaluated the impact of these autoantibodies on the developing fetal CNS and CNS vasculature.

It is unknown why some fetuses and neonates are susceptible to skin, blood vessel, and organ injury while others exposed to the identical maternal antibodies are healthy. There seems to be a complicated interplay between the timing and titers of autoantibodies, accessibility to target organs, and fetal factors that may contribute to inflammation and fibrosis. In the case of neonatal seizures, disruption of the blood-brain barrier that allows autoantibodies into the CNS may be a factor. The aforementioned autoantibodies are associated with vasculitis in adults, but it is unknown whether they are connected to lenticulostriate vasculopathy seen in infants who have NLS. Further studies are needed to determine whether this vasculopathy affects blood flow or has cytokine effects on downstream structures (basal ganglia, septum pellucidum, optic pathways, ventricles). The effect of maternal autoantibodies on neonatal microvascular structures, including choroid plexus and germinal matrix, has not been studied to date.

The cutaneous, hematologic, and hepatobiliary manifestations of NLS usually are mild and transient and typically disappear with the clearance of maternal antibodies from the neonatal circulation. If the disease is extensive (liver) or involves vulnerable tissues (eg, conduction tissues), the fibrosing injury can cause permanent dysfunction. Early diagnosis, close monitoring, and appropriate intervention with immunosuppressive treatment may subvert organ-threatening disease in select cases.

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NeoReviews Quiz

8. Neonatal lupus syndrome is caused by transplacental passage of maternal antinuclear and ribonuclear autoantibodies that target the fetal and neonatal tissues for immune destruction. Of the following, the *most* common manifestation of tissue injury in neonatal lupus syndrome is:

   A. Glomerulonephritis.
   B. Heart block.
   C. Hypothyroidism.
   D. Pneumonia.
   E. Thrombocytopenia.

9. A 7-day-old infant, whose birthweight was 1,480 g at an estimated gestational age of 37 weeks, has clinical and radiographic evidence of renal vein thrombosis. Maternal history is significant for systemic lupus erythematosus and previous pregnancy losses. The infant is breathing spontaneously in room air, receiving full enteral feedings, and has no other clinical manifestations such as skin rash, hepatosplenomegaly, or central nervous system disease. Of the following, the maternal autoantibody *most* likely to be associated with the clinical features in this infant is:

   A. Antinuclear SSA/Ro antibody.
   B. Antinuclear SSB/La antibody.
   C. Antinuclear U1RNP antibody.
   D. Antiphospholipid antibody.
   E. Antithyroid antibody.

10. Whereas neonatal lupus syndrome results from maternal autoantibodies, the primary infantile form of systemic lupus erythematosus results from the infant's own intrinsic deregulated immune system. Of the following, the *most* common manifestation of infantile systemic lupus erythematosus is:

    A. Aplastic anemia.
    B. Endocardial fibroelastosis.
    C. Interstitial pneumonitis.
    D. Lenticulostriate vasculopathy.
    E. Rhizomelic chondrodysplasia punctata.

11. Neonatal lupus syndrome accounts for 85% of all cases of congenital heart block. The heart block is attributed to a cascade of events triggered by the transplacental passage of maternal autoantibodies. Of the following, the initial event in the pathogenesis of congenital heart block is:

    A. Binding of maternal autoantibodies.
    B. Cardiocyte apoptosis.
    C. Fibrosis of the cardiac conduction system.
    D. Macrophage recruitment.
    E. Secretion of fibrosis-promoting factors.

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