# Neonatal Lupus Syndromes

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Neonatal lupus is an *in vivo* model of acquired autoimmune disease in which autoantibodies are transmitted from a mother with an autoimmune disease to her fetus through the placental barrier [1–7]. There is substantial evidence that autoantibodies, in particular those directed against the extractable nuclear antigens SSA/Ro and SSB/La, are pathogenetically linked to the clinical manifestations of the so-called neonatal lupus syndrome. The term neonatal lupus is in fact misleading since most of the mothers of affected infants are not affected by systemic lupus erythematosus, but by other autoimmune disorders including Sjogren's syndrome and undifferentiated connective tissue disorders, and a significant proportion of them are completely healthy.

The most important clinical feature of neonatal lupus is congenital heart block, which is usually complete (i.e., third degree).

## Epidemiology

Neonatal lupus is a rare disease, affecting males and females equally. According to the data of Michaelsson et al. [8], complete congenital heart block has an incidence of 1:20,000 live births; however these numbers include also CCHB associated with congenital anatomical malformations, and exclude *in utero* deaths. Because of the lack of national epidemiological registries, exact figures for the rarity of the disease are very difficult to obtain. The incidence of neonatal lupus substantially increases in a rheumatology practice, since about 1–2% of women with SLE will have an affected child, and the risk can at least double if one considers only anti-Ro/La positive mothers. However, prospective studies are difficult to conduct because about a third of the mothers are completely asymptomatic at the time of delivery, so that only after the birth of an affected child can the mother's autoantibody positivity be discovered. Recent long-term follow-up studies have shown that the long-term prognosis of these mothers is quite good, as many of them will not develop full-blown SLE but only minor symptoms such as arthralgia or sicca syndrome.

CCHB = complete congenital heart block
SLE = systemic lupus erythematosus

## Clinical Features

### Cardiac manifestations

CCHB is the most severe manifestation of neonatal lupus, being irreversible and carrying a high morbidity and mortality rate. The presence of signs or symptoms is mainly related to the ventricular rate, which usually ranges between 15 and 70 beats/minute; the lower the rate, the higher the possibility of fetal hydrops and neonatal cardiac failure.

CCHB is most frequently detected *in utero* by prenatal ultrasound between 18 and 24 weeks of gestational age. This "window" is related to the timing of transplacental passage of autoantibodies (which does not begin before the third month of gestation) and of the ontogenic development of the cardiac conduction system, which is not fully developed until about 22 weeks. In the majority of cases CCHB requires implantation of a pacemaker, frequently in the neonatal period. *In utero* death is usually related to intractable heart failure. Histologically, evidence of an inflammatory cellular infiltrate can be present if death occurs close to the time bradycardia is first detected, but in later stages calcification of the conductive system might be the only pathologic finding. The first lesion might therefore be a pancarditis, subsequently resulting in fibrosis of the conducting system clinically manifest as permanent heart block.

Other cardiological manifestations have been reported, such as congenital malformations, often in association with CCHB, incomplete blocks, and more recently sinus bradycardia, which we encountered and subsequently reported [9,10]. This last finding is of importance, as it suggests that not only the atrioventricular node but also the sinus node can be affected.

Another recent experience from our group has shown a high incidence of QT prolongation in infants of mothers with anti-SSA/Ro antibodies [11]. We in fact analyzed 21 electrocardiograms from anti-Ro-positive infants and 7 from anti-Ro-negative infants born of mothers with autoimmune diseases, and measured the QT interval corrected for heart rate. The mean corrected QT interval was significantly longer in anti-Ro-positive than in anti-Ro-negative infants ($P=0.001$). Nine of 21 Ro-positive infants and none of 7 Ro-

negative infants had a QTc value above the upper normal limit (440 msec). A 24 hour ECG recording was performed in five patients and confirmed the QT prolongation. Since a prolonged QTc is associated with increased risk of sudden death in the first year of life, these infants were subsequently treated with a beta-blocker in order to prevent arrhythmias. These findings suggest that infants born of mothers with anti-Ro antibodies should be monitored with ECGs during their first months of life.

### Skin involvement

A skin rash can be present in the neonatal period, but more frequently it appears between the second and third month of life [12]. Unlike CCHB, it is transient and disappears with the clearance of maternal autoantibodies from the baby's circulation, usually without any residua. The rash is erythematosus and scaly, similar to subacute cutaneous lupus erythematosus. It is frequently annular in shape, and mostly located in sun-exposed areas, with a characteristic predilection for the periorbital area. Ultraviolet exposure may be an initiating factor and can exacerbate an existing rash. Histologically the lesions are similar to subacute cutaneous lupus, with hyperkeratosis, epidermal atrophy, basal degeneration, interstitial edema, and perivascular mononuclear infiltrate. Immunoglobulin and complement deposition has been demonstrated by direct immunofluorescence at the dermo-epidermal junction. Since these lesions are self-limiting, treatment is usually not required.

### Laboratory abnormalities

Hematological abnormalities have been described, usually consisting of anemia and/or thrombocytopenia [13]. In our prospective series of 20 children followed during their first year of life with periodic clinical and laboratory evaluations, we detected a high incidence of anemia. Half of the newborns and 4 of 15 infants at age one month had a hemoglobin value lower than 2 standard deviations for age. The mean hemoglobin value, which was initially below the minimum for age, gradually returned to normal, presumably in coincidence with the disappearance of autoantibodies.

Hepatic involvement has also been described [14,15], varying from an asymptomatic increase in serum transaminases to severe cholestasis. In some cases this was noted at birth but was not clinically evident until several weeks in others. As for skin rash and unlike CCHB, these manifestations are transient and usually do not need medical treatment.

## Pathogenesis

Neonatal lupus is an interesting model of autoimmune disease. Indeed, current evidence suggests that the clinical manifestations are not only associated with but causally related to the presence of autoantibodies, in particular those directed against the extractable nuclear antigens SSA/Ro and SSB/La [16–21].

The connective tissue diseases are frequently associated with antinuclear antibodies and, among the individual self-proteins targeted by ANA, SSA/Ro and SSB/La are found in a very high percentage of patients with SLE and Sjogren's syndrome. SSA/Ro — a complex antigen system whose function is not completely known — comprises at least two polypeptides of 52 and 60 kD molecular weight respectively. Although there is no specific antibody profile for mothers of children with CCHB, it seems that the combination of anti-52 kD Ro and anti-La confers the highest risk of delivering an affected child.

Genetic factors may also play a role in this disease, and HLA associations have recently been studied in order to identify susceptibility alleles for CCHB, but no unique HLA profile in mothers or children could be found [22–24].

In most cases of isolated CCHB, anti-Ro antibodies are present in the mother's serum. Experimental data, both in animal models and in *in vitro* studies, have suggested the pathogenicity of these autoantibodies. In the first study by Alexander et al. [25], arrythmogenic effects of anti-Ro/La antibodies were reported in newborn rabbit ventricular papillary muscles. Subsequently Kalush et al. [26] showed that offspring of BALB/c mice with experimental SLE had a high percentage of defects in their conductive system, and Garcia et al. [27] confirmed these findings in adult rabbit hearts, also demonstrating an effect on peak slow inward calcium currents in patch-clamp experiments. More recently, Boutjdir et al. [28,29] conducted two more detailed studies of the arrythmogenic potential of anti-Ro. In the first, performed in the working human fetal heart, the pathogenicity of anti-Ro antibodies on CCHB was explained by inhibition of L-type calcium currents, while in the second the arrythmogenic effects were demonstrated in a rat heart model, with action potential recording from AV nodal preparations.

Finally, compelling evidence of pathogenicity by anti-Ro is provided by Reichlin et al. [30], who showed in tissue eluates from a child who died with CCHB that antibodies to native 60-kD and denatured 52-kD Ro/SSA were enriched only in the eluate from the heart and not from other organs.

The pathogenicity of autoantibodies is also supported by the fact that, except for CCHB, clinical manifestations such as skin rash disappear in a temporal relationship with clearance of antibodies from the baby's circulation. The exact pathogenetic mechanism is still unknown, but a direct electrophysiologic effect by the autoantibodies on the conductive system and an indirect effect subsequent to a myocarditis have been hypothesized.

However, several issues have yet to be explained, such as why only a minority of mothers with anti-Ro and La deliver an affected child, and why heart block almost always affects only the fetus and not the mother. Also intriguing is the discordance of the disease in monozygotic twins [31,32]. All these findings suggest that other unknown factors, maternal and/or fetal, play a role in the disease pathogenesis.

QTc = corrected QT interval

ANA = antinuclear antibodies

## Prognosis

CCHB is a severe disease. Mortality, usually *in utero* or in the first 3 months of life, can reach 30% even after intensive and supportive care. In a recent update of the U.S. national neonatal lupus registry [33], pacemakers were required in 63% of live-born children (52% within 9 days, 22% within 1 year, and the rest after 1 year of age). A recent report [34] stated that prophylactic pacemaker treatment should be recommended even in asymptomatic patients because of the high incidence of unpredictable Stokes-Adams attacks and significant morbidity and mortality.

For prenatal counselling it is important that the mother of a patient be aware that she might deliver a second affected child. There are few prospective studies on this issue, but the possibility seems to be between 10 and 20% — not very high but substantially higher than for the first pregnancy.

The mothers of affected children who at the moment of delivery are asymptomatic do not seem to have a bad prognosis. Recent studies have shown that, at the most, half the mothers of children with CCHB eventually develop a connective tissue disease, which is mild and not life-threatening in most cases [35–38].

Finally, the possibility for a child with neonatal lupus to develop SLE or another connective tissue disease in later life seems to be extremely rare [39]. Only a few cases, usually young females, have been described; therefore the risk might not be higher than in asymptomatic children of mothers with autoimmune diseases, or even in the general population.

## Treatment

There is no known effective therapy for CCHB. Prenatal interventions are substantially related to drug therapy for the mother in order to diminish the autoimmune response and/or the cardiac inflammatory injury, and to increase fetal heart rate.

Corticosteroids have been used, in particular dexamethasone which is not inactivated by the placental enzymes [40]. However, since CCHB is irreversible and because of possible side effects such as oligohydramnios and adrenal suppression, therapy should be instituted only if the block is incomplete or of recent onset, or if a complete block is accompanied by signs of fetal distress such as hydrops, effusions, ascites, or heart failure. Dexamethasone (4 mg/day) should be discontinued anyway after several weeks if no benefit is obtained.

A non-immunologic approach with sympathomimetics has also been tried. Groves et al. [41] administered isoprenaline and salbutamol to three mothers of fetuses with CCHB, without reversal of the block but with increase in heart rate, improvement in ventricular function, and resolution of fetal hydrops with salbutamol. This drug could therefore be considered in cases of CCHB with deteriorating cardiac function.

Postnatal treatment of complete heart block is based on pacemaker implantation. Frequently this has to be done in the neonate, initially through an electrocatheter that is introduced in the ventricle by femoral vein percutaneous injection. The ventricle is then stimulated at a frequency of 90–110 beats/minute. This temporary approach allows an improvement in clinical status in order to tolerate a permanent pacemaker implantation without significant risks. Due to the very low weight of these subjects, often <2.5 kg, the pacemaker is implanted by the thoracotomic or sternotomic route, with an electrode on the epicardial surface which is connected to an impulse generator placed in an abdominal subfascial pouch. In the presence of extreme bradycardia or arrhythmia, cardiac drugs such as isoproterenol (0.1–0.3 μg/kg/min) or lidocaine (1 mg/kg i.v.) need to be administered as well.

Non-cardiac manifestations such as skin rash or hematological abnormalities usually do not require any treatment, since they are reversible and disappear spontaneously, usually during the second semester of life.

## Conclusions

Pregnant women who carry anti-Ro/La antibodies are at risk of delivering a baby with congenital heart block or other minor clinical manifestations. This group includes patients affected not only with SLE, but with other connective tissue diseases as well, and a significant percentage of asymptomatic women. In the presence of complete heart block it is mandatory to perform immunological screening for the presence of autoantibodies in both the mother and the child. Transplacentally acquired autoantibodies seem to play a role in the disease pathogenesis, possibly binding to autoantigens in the developing fetal heart and/or eliciting an inflammatory tissue injury. Patients with CCHB are at high risk of perinatal death and often require pacemaker implantation. Due to the rarity of the disease, important issues such as optimal therapeutic protocols might be obtained only with the creation of national or international registries.

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## Capsule

### Iron metabolism

The transferrin receptor (TfR) delivers transferrin-associated iron into cell for use in a variety of physiological processes, including cell growth. The receptor also binds HFE, the protein that is defective in human hereditary hemochromatosis, an iron storage disease that affects 1 in 300 individuals of northern European origin. Lawrence et al. determined the three-dimensional crystal structure of the extracellular domain of TfR. The structure revealed a monomer of three domains, one of which resembles carboxy- and aminopeptidases. This work provides a structural foundation for future studies of how iron uptake and release are controlled in the cell.

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