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Review

Neonatal lupus: Follow-up in infants with *anti*-SSA/Ro antibodies and review of the literature

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ABSTRACT

Neonatal Lupus Syndrome (NLS) is a distinct clinical entity caused by transplacental passage of maternal *anti*-SSA/Ro antibodies (Ab). Mothers may have systemic lupus erythematosus, Sjögren syndrome, or other connective tissue disease, or may be completely healthy at the time of giving birth. NLS includes several clinical manifestations: complete congenital heart block (CCHB) and cutaneous lupus are the most common, while hepatobiliary disease, hematological manifestations and central nervous system involvement may occur.

Data from literature on the incidence of the different clinical manifestations of NLS are difficult to compare because they come mostly from retrospective studies or prospective studies, but up to date no systematic follow-up was carried out. We performed a large prospective single-center study with a systematic clinical and instrumental follow-up until 9 months of life, in order to evaluate the incidence and the clinical impact of NLS features.

From 2004 to 2014 all infants born in our center to mothers with *anti*-SSA/Ro Ab were enrolled in a specific diagnostic and follow-up (FU) program.

At birth, 50 infants born to mothers with *anti*-SSA/Ro Ab were found positive for anti-SSA/Ro Ab. Infants were tested for anti SSA/Ro Ab at 3 months of life, if positive they were re-tested at 6 and 9 months. At 9 months *anti*-SSA/Ro Ab were positive in 10% of children. In two cases (4%) a CCHB was identified during pregnancy and required pacemaker implantation at birth. In 10% of cases a transient ECG alterations was found during follow-up. Hematological NLS features (anemia, neutropenia, thrombocytopenia) were found at birth and during FU in several patients, in all cases without clinical manifestations and in most cases with complete normalization at 9 months. Mild and transient elevation of aminotransferases between 3 and 6 months of life were found in 56% and 40% of patient, respectively; non-specific ultrasound cerebral anomalies in absence of clinical neurological signs were found at birth in 9 patients (18%), subsequently normalized.

Prenatal maternal screening is of primary importance in order to early detect CCHB, which requires maternal treatment and pacemaker implantation at birth. Infants born to mothers with *anti*-SSA/Ro Ab should be monitored for all NLS features at birth. However, during the first months of life, these infants seem to develop only mild, transient and self-limited clinical manifestations, which in most cases are completely solved at 9 months of life. This consideration, together with the evidence that only 10% of infants had *anti*-SSA/Ro Ab persistent in blood at 9 months, suggests that follow-up of these children can be performed until 6–9 months of life with good clinical safety. Moreover, a clinical and laboratory monitoring at 3 months of life, when the highest incidence of hematological features and liver tests alterations are observed, is strongly recommended. In the future, it would be clarified if a follow-up until adulthood would be indicated in cases with persistent anti SSA/Ro or in all infants born to mother with anti SSA/Ro.

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1. Introduction

Neonatal Lupus Syndrome (NLS) is an acquired autoimmune disease caused by transplacental passage of maternal *anti*-SSA/Ro and/or anti-SSB/La autoantibodies [1–5].

Mothers may have systemic lupus erythematosus (SLE), Sjögren syndrome (SS), other connective tissue disease, or may be completely healthy at the time of giving birth. The laboratory hallmark of the disease is the presence of *anti*-SSA/Ro antibodies [6].

NLS includes several clinical manifestations: congenital heart block (CHB) and cutaneous lupus are the most common, while hepatobiliary disease, hematological manifestations and central nervous system (CNS) involvement may occur [7]. Rectal bleeding and plantar atrophy are also reported [8]. The non-cardiac manifestations of NLS are most transient and resolve as maternal antibodies are cleared from the neonatal circulation, while a complete atrio-ventricular block in a structurally normal heart is considered permanent [9].

The skin rash is highly characteristic and it may be rarely present at birth, but it appears more frequently in the second and the third month of life [10]. This rash is most common on the head and neck, which are most exposed to ultraviolet rays [11]. Hepatobiliary involvement is described between 10% and 25% of NLS cases and it may cause congenital liver failure, cholestasis or a late and transient increase of transaminases [12–14]. Hematological manifestations of NLS may be anemia, neutropenia, thrombocytopenia [15,16].

CNS involvement in newborns is possible but uncommon. Few reports are available and frequency and different patterns of CNS findings are not exactly known [17–19].

Data from literature on the incidence of the different clinical manifestations of NLS are difficult to compare, because they come mostly from retrospective studies or prospective studies, but in which no systematic follow-up was carried out [20]. Few data are also available for the follow-up of children with NLS [21].

We performed a large prospective single-center study with a systematic clinical and instrumental follow-up until 9 months of life, in order to evaluate the incidence and the clinical impact of NLS features and their correlation with *anti*-SSA/Ro Antibodies (Ab).

2. Materials and methods

Since 2004 to 2014 all infants born to mothers with anti-SSA/Ro antibodies (Ab) in our center were enrolled in a specific diagnostic and follow-up program. Follow-up evaluation was performed at 3, 6 and 9 months of life in infants with persistent *anti*-SSA/Ro Ab and/or important clinical manifestations.

For each infants, data on the mother diagnosis and therapy before and during pregnancy, and data on the pregnancy outcome with particular interest for the laboratory and instrumental tests (level of *anti*-extractable nuclear antigens [ENA] Ab, ultrasound evaluation of fetal growth, fetal echocardiography, Doppler velocimetry of maternal and fetal vessels, non-stress test and hemochromocytometric and blood clotting tests) were collected.

At birth and during follow-up, clinical and anthropometric data were recorded, and the following tests were performed:

- Anti ENA Ab detected by ELISA [22]:
  - Anti-SSA/Ro, *anti*-SSB/La (normal values <25 U/ml)
  - Anti-RNP (normal values <9 U/ml)
  - Anti Sm (normal values <25 U/ml)

- CBC with differential white cell count
- SGOT, SGPT, γGT
- Cerebral ultrasonography
- Electrocardiography (ECG) and echocardiography.

According to the descriptions reported in the literature, the following clinical and laboratory signs have been considered typical of the NLS:

- Heart manifestations
  - Atrioventricular block of any degree
  - Late conduction
  - Dilatative cardiomyopathy

- Hepatobiliary manifestations
  - Liver failure (with clinical signs of liver damage due to hemochromatosis)
  - Jaundice (with high conjugated bilirubin)
  - Increased serum level of liver enzymes SGOT (normal values <45 U/l), SGPT (normal values <45 U/l), γGT (normal values <90 U/l), alkaline phosphatase (normal values <110 U/l)

- Haematologic manifestations
  - Anemia (hematocrit <30%)
  - Thrombocytopenia (platelets <100.000/μl)
  - Neutropenia (neutrophil <1000/μl)

- Skin manifestations
  - Rash in the shape of large annular spots of squamous erythema, hypopigmeted areas, mainly located on the face, in the periorbital area, and on the scalp

- Echoencephalographic abnormalities
  - Lenticulostriate vasculopathy
  - Pseudocystis of the choroid plexus.

3. Results

Fifty infants born to mothers with *anti*-SSA/Ro Ab were found positive for anti-SSA/Ro Ab in the first day of life. The prevalence of infants born to mothers with anti-SSA/Ro Ab observed at our hospital was 0.25% of the maternal-newborn population. General features of the infants are shown in Table 1. Seventeen infants were positive for anti