

Neonatal lupus – case series of a tertiary hospital

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ABSTRACT

Neonatal lupus (NL) is a very rare condition with an estimated incidence of 1 in 20.000 pregnancies. It is caused by the transplacental passage of autoantibodies anti-Ro/SSA, anti-La/SSB antibodies and/or anti-U1 RNP antibodies into the fetal circulation. The mother may be completely asymptomatic or have a known inflammatory rheumatic disease, such as Sjögren syndrome (SS) or Systemic Lupus Erythematosus (SLE). Clinical manifestations are diverse, being the most common cutaneous and cardiac. The authors present a case series of eight cases diagnosed with NL between January 2008 and December 2016 in a tertiary hospital and a brief revision of the literature.

Keywords: Anti-U1 RNP antibodies; Neonatal lupus; Anti-La/SSB antibodies; Anti-Ro/SSA antibodies.

INTRODUCTION

Neonatal lupus (NL) is an autoimmune disorder with different manifestations. Cutaneous and cardiac manifestations are the most common and may coexist in 10% of cases, being the first one more harmless¹⁻³. Usually, NL is observed at birth but the skin lesions may appear only during the first weeks of life. Their mothers have positive autoantibodies anti-Ro/SSA (90% of the cases), anti-La/SSB and/or anti-U1 RNP⁴.

Diagnosis of NL requires a high level of suspicion. It is made by clinical examination or complementary diagnostic tests (for instance, echocardiography or electrocardiography) and laboratory demonstration of NL-associated antibodies in the mother and/or child.⁴ The

diagnosis might be presumptive, if there is a typical cutaneous presentation with unknown etiology.⁵

We present a review of 8 cases diagnosed between January 2008 and December 2016 in the Neonatal Unit or followed in outpatient departments in Centro Hospitalar de São João (CHSJ), Porto (Table I).

CASE REPORTS

CASE 1

Female newborn (NB) with prenatal diagnosis (PND) of complete heart block (CHB). Her mother had ANA 1/1000 speckled pattern, Anti-dsDNA <10.0 UI/mL, anti-Ro/SSA positive and was assumed as having a probably Sjögren syndrome (SS), despite the absence of symptoms. In the past, this woman underwent to a salivary gland biopsy, with inconclusive result, and to a salivary gland scintigraphy, which showed a decreased salivary secretion. She was treated with salbutamol, dexamethasone, hydroxychloroquine (HCQ) 200 mg and intravenous immunoglobulin (IVIG) during pregnancy. After birth, the child was admitted to the Neonatal Intensive Care Unit (NICU), where a pacemaker was implanted (Figure 1). Almost 2 years later, the child has ascending aortic dilatation (18mm) without other structural cardiac abnormalities and developed no further complications.

CASE 2

Female NB with PND of CHB (Figure 2) and suspected pulmonary valve stenosis. Consequently, her mother was diagnosed with Systemic Lupus Erythematosus (SLE) in the last week of gestation, not receiving any treatment during pregnancy. She had ANA 1/320 nucleolar pattern, anti-dsDNA 0.5 UI/mL, anti-Ro/SSA and anti-La/SSB positive and iron deficiency anaemia unresponsive to oral iron. The NB was admitted to NICU, where she received a definitive pacemaker and pulmonary valve stenosis was excluded. On day 2 she had thrombocytopenia, abnormal liver function tests and positivity for anti-Ro/SSA and La/SSB. At the age of

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TABLE I. CLINICAL AND LABORATORY CHARACTERISTICS

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 |
|----------------------------|----------|------------------|------------------|----------|------------------|------------------|------------------|------------------|
| Gender | F | F | M | F | F | F | M | M |
| Maternal history | SS | SLE | SLE | SLE | SS | SS | SS, SLE | SS |
| Dermatological involvement | No | No | No | No | No | No | Yes | Yes |
| Cardiac involvement | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No |
| Other organ involvement | No | Yes | Yes | No | No | No | No | No |
| Child's autoantibodies | NE | Anti-SSA and SSB | Anti-SSA | NE | NE | Anti-SSB | Anti-SSA and SSB | NE |
| Maternal autoantibodies | Anti-SSA | Anti-SSA and SSB | Anti-SSA and SSB | Anti-SSA | Anti-SSA and SSB | Anti-SSA and SSB | Anti-SSA and SSB | Anti-SSA and SSB |

F: Female; M: Male; SS: Sjögren Syndrome; SLE: Systemic Lupus Erythematosus; NE: Not Evaluated

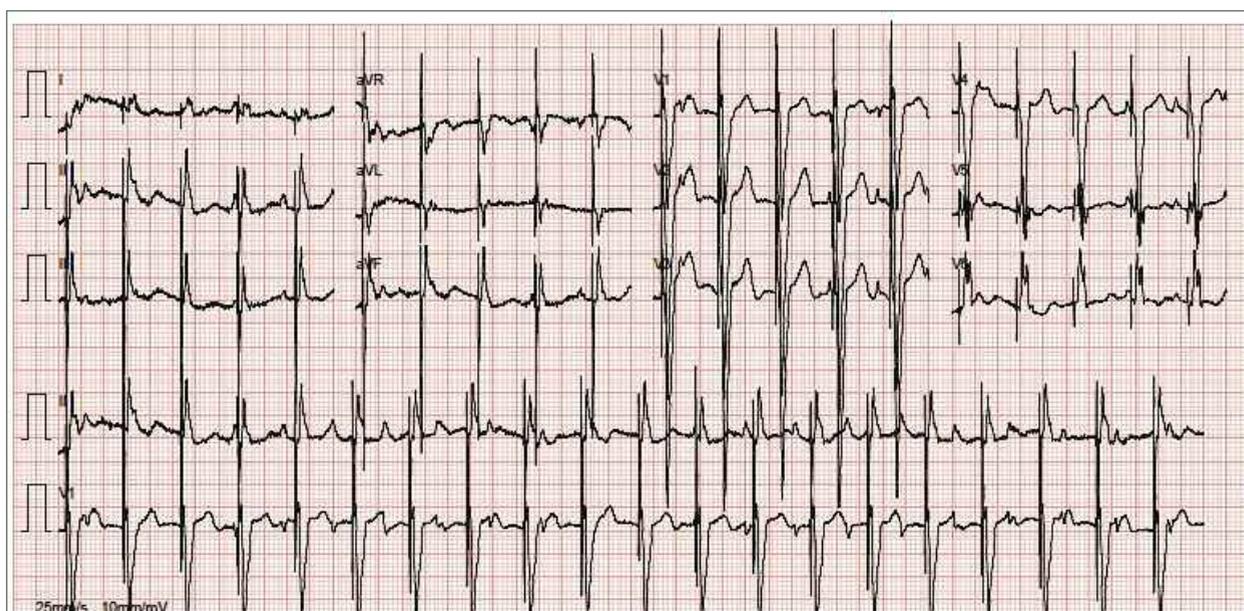


FIGURE 1. Case 1; Electrocardiogram – Evidence of ventricular pacing (spike) previous to each QRS complex

8 months, dilated cardiomyopathy with an ejection fraction of 21%, pericardial effusion and a lupus myocarditis was diagnosed. Despite medical treatment, she died at age of 2 from cardiac heart failure.

CASE 3

Male NB with PND of CHB and mild to moderate cardiomegaly. This was the brother of case 2 and their mother maintained anti-Ro/SSA and anti-La/SSB positivity. She was treated with prednisolone and HCQ during pregnancy, and she started salbutamol 32mg/d and dexamethasone 8 mg/d on week 26. NB was also

admitted to NICU where he underwent pacemaker placement. Echocardiogram didn't show heart abnormalities. At day 23, he developed hypoxemic respiratory failure and required mechanical ventilation. He didn't respond to antibiotics and no infectious agents were found. The chest radiograph showed bilateral interstitial infiltrates (Figure 3), characterized as ground glass opacities in chest CT scan. A diagnosis of lupus pneumonitis was presumed and he received IV methylprednisolone with clinical improvement. He was positive for anti-Ro/SSA. He is now 14 months and has had a favourable evolution.

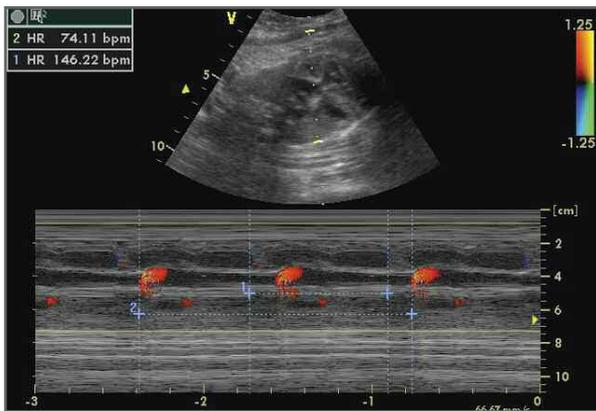


FIGURE 2. Case 2; Color M-mode fetal echocardiography with evidence of complete heart block (CHB); 1 – Atrial Heart Rate (HR), 2 – Ventricular Heart Rate

CASE 4

Female NB with PND of bradyarrhythmia. The mother had anti-Ro/SSA positive and ANA 1/1000 speckled pattern but was asymptomatic, and only developed SLE four years later. The NB is one of two twins. In the NICU, she was diagnosed with first-degree AV block with episodes of second-degree AV block. Her sister didn't have any NL manifestations. Currently, this girl is 5 years old, asymptomatic and is followed by Pediatric Cardiology. She never required pacing and maintains first-degree AV block.

CASE 5

Female NB with a PND of CHB. The mother has SS with ANA 1/320 speckled pattern, anti-Ro/SSA and anti-La/SSB positive. After she was born, she was admitted to NICU. She is currently 8 years old and she was always asymptomatic, never requiring pacing. She presents left auricular and ventricular dilatation, mild mitral and aortic insufficiency with a normal ejection fraction and an enlargement of the pulmonary trunk. Five years later, her mother remained anti-Ro/SSA positive and delivered a girl without any NL manifestations.

CASE 6

Female NB with a PND of CHB. The mother had ANA 1/1000 speckled pattern, anti-Ro/SSA and anti-La/SSB positive. She was treated with salbutamol and dexamethasone but just diagnosed with SS months after pregnancy, when symptoms appeared. The NB was admitted to NICU and required pacemaker placement. The NB had ANA 1/320 speckled pattern and positive anti-La/SSB. She currently has mild tricuspid insufficiency

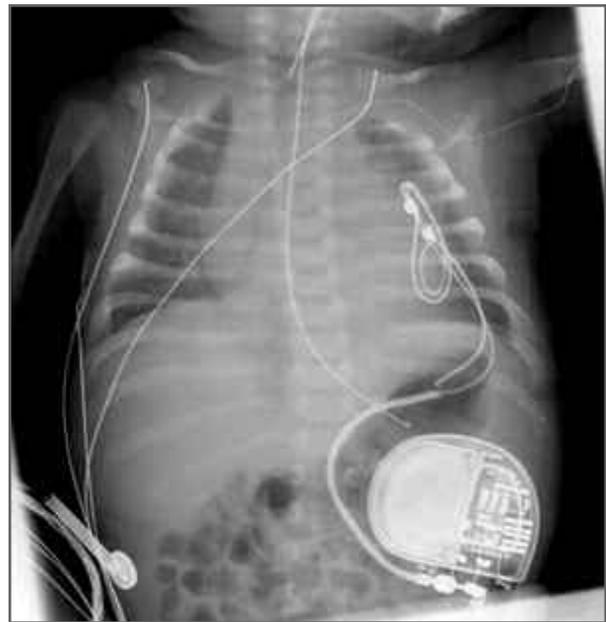


FIGURE 3. Case 3; Chest radiograph at day 24 with bilateral interstitial infiltrates

and is followed by Pediatric Cardiology. Two years later, this mother had a girl without any NL manifestation.

CASE 7

Male NB born at term by elective caesarean section. Due to bradycardia he was admitted to NICU, where a mild facial rash was also identified. He was discharged at day 3 after spontaneous resolution of bradycardia, echocardiogram did not show any abnormalities. His mother has SS/SLE overlap, with ANA 1/1000 homogenous pattern, anti-dsDNA 162.6 UI/mL, anti-Ro/SSA and anti-La/SSB positive. She was treated with HCQ and aspirin during pregnancy. The child had ANA 1/320 speckled pattern, anti-Ro/SSA and anti-La/SSB positivity. The skin lesions worsened progressively, becoming a malar rash and a maculopapular rash on scalp, neck, trunk and abdomen (Figure 4). Skin biopsy showed vacuolar degeneration of basal layer, perivascular inflammatory lymphocytic infiltration of the superficial dermis and dermal mucinous deposits with normal direct immunofluorescence, which corresponds to NL diagnosis. He was treated with 1% topical hydrocortisone and the lesions disappeared without sequel.

CASE 8

Male NB had a malar rash at birth. His mother has SS,



FIGURE 4. Case 7; Malar rash and maculopapular rash on trunk

with ANA 1/1000 speckled pattern, anti-dsDNA <10.0 UI/mL, anti-Ro/SSA and anti-La/SSB positive. She was treated with HCQ and aspirin. During the pregnancy, she also developed hypothyroidism and received levothyroxine from week 27. At 1 month of age, he was evaluated by Dermatology due to worsened malar rash, which became annular and erythematodesquamative. After treatment with 1% topical hydrocortisone, the lesions resolved completely within 5 days. Given the favourable outcome, no further tests were performed.

DISCUSSION

NL is a rare disease with an estimated incidence of 1 in 20.000 pregnancies, but it seems to be underdiagnosed. On one hand, it is possible that mothers don't have an inflammatory rheumatic disease. On the other hand, cutaneous manifestations may mimic rash from other causes and some other manifestations are mild, transient and might go unnoticed. Even if noticed, the

attribution of manifestations to NL may be difficult^{5,6}. Cutaneous NL has a female predominance, with a female-male ratio of 2:1 to 3:1.⁷ Cardiac NL has an equal female-male distribution⁴.

It is accepted that the transplacental passage of these IgG autoantibodies from the second trimester is responsible for the appearance of NL⁸.

Approximately 40-60% of mothers are asymptomatic or without known autoimmune diseases when the infants are diagnosed with NL, as we verified in cases 1, 2, 4 and 6. 50% of them will later develop symptoms related to autoimmunity, like in case 4^{4,5,9}. Mothers may have SLE, SS, rheumatoid arthritis, mixed connective tissue disease and undifferentiated connective tissue disease^{4,5}. In our series, mothers had as much SLE as SS (Table I).

Although 98% of NL cases are positive for anti-Ro/SSA, La/SSB and U1RNP, just 1-2% of the women with these antibodies have neonates with the disease⁴. In subsequent pregnancies, this incidence is higher, around 25%. In women with anti-Ro/SSA or anti-La/SSB antibodies, recurrence of CHB in subsequent pregnancies is 15%.⁵ In this case series, three women had subsequent pregnancies: two women with anti-Ro/SSA and anti-La/SSB positivity, but just one had a child with NL, and another woman with anti-Ro/SSA positivity, who had a healthy child.

In fact, only some neonates exposed to the antibodies developed NL. Perhaps other factors may predispose for the disease, like the titers of maternal antibodies, genetic predisposition and environmental factors. In case 4, a dizygotic twin pregnancy resulted in just one affected fetus, which might be genetically susceptible⁴.

Cutaneous lesions usually appear between the 4th-6th week of life, but may be present at birth¹⁰. They consist of multiple red macules that evolve by clearing the center and developing an annular configuration². Typically, they are localized in photoexposed areas, like the head or neck, but may also occur on the trunk or the extremities^{2,3}. If the periorbital area is affected, a typical signal named "raccoon eyes" or "owl eyes" is originated¹⁰. They resolve within 4-6 months, when maternal autoantibodies disappear from the circulation. Very rarely, it remains as permanent telangiectasia.³ Despite the spontaneous resolution, treatment may include sun avoidance, sunscreen and mild topical steroids, as in cases 7 and 8^{2,3}. It is important to establish the differential diagnosis with other pathologies like atopic dermatitis and neonatal acne³. Skin

biopsy is only necessary when there is doubt about the NL diagnosis⁵.

Heart involvement is mostly diagnosed between 18-24th weeks of gestation. It is a potentially life-threatening complication, with a mortality rate of 15-30%, especially during fetal, neonatal and infant periods¹¹. The CHB is most commonly associated with maternal anti-Ro/SSA antibodies with or without anti-La/SSB, as in our 6 cases of cardiac involvement^{11,12}. The autoantibodies induce inflammation and fibrosis of atrioventricular node¹². Depending on the degree of scarring, the AV block severity is different. First and second-degree AV blocks may reduce its degree or even resolve completely, but third-degree is irreversible¹¹.

Some individuals may develop other severe complications such as valvular insufficiency or endocardial fibroelastosis that may progress to end-stage heart failure and death. Recently, an association between CHB in NL and aortic dilatation has been reported, as in case 1¹². Furthermore, some authors described a diffuse myocardial disease, before or after birth, and isolated cardiomyopathy, like in case 2¹¹.

After the PND of AV block, it is advisable to start dexamethasone/betamethasone and/or IVIG therapy, due to their potential benefit in reversing first or second degree block and preventing the development of CHB in foetuses, respectively. In our case report, 3 cases were treated with dexamethasone and 1 with also IVIG but they maintained the CHB since the block was already established. Several studies had found that, if foetal ventricular rate <50-55 beats/min, there is profit in adding a sympathomimetic¹¹.

Recently, has been suggested a role of Toll-like Receptors (TLR) in the pathogenesis of cardiac-NL. Consequently, HCQ, an inhibitor of TLR ligation, has been studied in women with SLE. Results demonstrated that HCQ prevents disease flare during pregnancy and, in patients with anti-Ro/SSA antibodies and previous child with cardiac NL, HCQ may reduce the recurrence of cardiac NL in subsequent pregnancies^{8,13}. In case 1 and 3, HCQ couldn't prevent the appearance of CHB but, in case 7 may played a role in reversing bradycardia. Case 8 only had cutaneous manifestations.

Newborns with cardiac involvement should be admitted to NICU, as we verified in this case series. It is known that 63% of all recognized cases of AV block require pacemaker implantation, which happened in 4 of our 6 cases of cardiac involvement¹¹.

The hepatobiliary system may also be affected, with

only asymptomatic and transient elevation of liver function tests, such as in case 2, or with severe liver failure^{4,10}.

Hematological abnormalities occur in 10-35% of the NL cases. It may include thrombocytopenia (like in case 2), neutropenia and anemia, isolated or in any combination, which resolve within days to months⁶.

The central nervous system (CNS) is only affected in 1.4% of patients with NL. It is most commonly asymptomatic and neuroimaging-determined¹⁴.

Very rarely, the respiratory system may be affected with a pneumonitis-like presentation, like in case 3.⁴

There is no doubt that early detection of this condition is paramount, especially when there is cardiac involvement, since adequate treatment may reverse lower grade HB. Pregnant woman with anti-Ro/SSA and anti-La/SSB should be referred to experienced centres early on, since surveillance with serial echocardiography and ultrasonography is fundamental, as is adequate treatment of the maternal underlying condition.

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