

CONCISE REPORT

Late neonatal lupus erythematosus onset in a child born of a mother with primary Sjögren's syndrome

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Background: The neonatal lupus syndrome can be present as congenital heart block (CHB) or as neonatal lupus erythematosus (NLE), both seldom passively acquired autoimmune diseases. CHB starts around week 20 of pregnancy and is a lifelong event, whereas NLE is self limiting and usually starts at the 6th week of the child's age—the maximum recorded up to week 20.

Case report: An asymptomatic mother with primary Sjögren's syndrome and anti-SSA/Ro52, anti-SSA/Ro60, and anti-SSB/La autoantibodies is described who, at gestational week 23 during her first pregnancy, was diagnosed as having a male fetus with CHB due to third degree atrioventricular block. The boy from the second pregnancy developed skin eruptions which clinically and by biopsy were compatible with NLE at week 20+1 post partum.

Conclusions: Our case of NLE, starting at week 20+1 of age, seems to be the latest reported clinical case of NLE. Development of CHB and NLE in two consecutive boy pregnancies is unusual.

- The very late development of NLE in a 20+1 week old boy, second child of a mother with circulating anti-Ro/La autoantibodies with primary SS.
- The development of CHB in a male fetus in gestational week 23 of her first pregnancy. A caesarean section was planned for week 38 but the fetus was found dead 2 days before. A necropsy did not show any other obvious cause.
- The occurrence of both forms of NLS in the first two pregnancies of a patient with primary SS at a stage where the mother thought she was healthy.

MATERIAL AND METHODS

Mother

The mother was born in 1966 without siblings, and with no known heredity of connective tissue or rheumatic diseases. Her childhood and adolescence was uneventful apart from acne rosacea since 1991. Otherwise she had been healthy, and especially had no infectious or skin abnormalities.

First pregnancy

In her first pregnancy the routine control examination in week 19 was normal. At week 23 the midwife detected a fetal bradycardia, pulse 60. Next day ultrasonography and fetal echocardiography showed third degree atrioventricular heart block. A caesarean section was planned at week 38+0 but 2 days before the fetus died intrauterinely. A male fetus, 2,780 g and 48 cm, was delivered vaginally in February 2000. A necropsy did not find hydrops or macroscopic organ abnormalities. In particular, the heart chambers and valves were normal. Microscopic examinations of most organs were normal. However, no immune reactions were performed.

Her second pregnancy was uneventful and in March 2001 a healthy boy, 3,490 g and 49 cm, was born. He was breast fed. At week 20+1—after a sunny day—the boy developed swelling and erythema periorbitally and less intense of the cheeks and forehead. The scalp with hair, the extremities, the trunk, and the oral cavity were normal. A biopsy showed hypotrophic epidermis with spongiosis and basal infiltration of leucocytes with karyorrhexis haematoxylin bodies. Some follicular hyperkeratosis and, perivascularly, lymphocytic infiltrates were seen. Immunofluorescence showed deposition of IgM and C3, and IgG deposition in the basal and suprabasal layer but not in the dermoepidermal junction zone.⁹ The changes seen are thus compatible with NLE and part of the NLS.

No new flares occurred and the skin lesions healed spontaneously without hypo-/hyperpigmentation or scarring.^{2 10} Blood samples showed leucocytes at $120 \times 10^{12}/l$ —normal for age. Values for other blood elements, antinuclear antibodies (ANA), anti-DNA, IgM rheumatoid factor, anti-RNP,

Abbreviations: ANA, antinuclear antibodies; CHB, chronic heart block; NLE, neonatal lupus erythematosus; NLS, neonatal lupus syndrome; SS, Sjögren's syndrome

Neonatal lupus syndrome (NLS) occurs rarely perinatally as two distinct clinical presentations, either as lifelong isolated congenital heart block (CHB) and/or as cutaneous vasculitis with a pathology resembling subacute cutaneous lupus erythematosus. Consequently, it is named neonatal lupus erythematosus (NLE). The clinical manifestations of NLE can start perinatally^{1 2} until week 20 after birth; a mean of 6 weeks was found in a group of 57.¹ Both diseases are believed to be initiated by circulating maternal anti-SSA/Ro and/or anti-SSB/La IgG1 autoantibodies. The former autoantibody occurs as two separate forms, anti-SSA/Ro60 kDa and anti-SSA/Ro52 kDa, the latter occurs as anti-SSB/La48 kDa. In a recent study of nine anti-Ro/La autoantibody positive mothers who previously gave birth to children with CHB, it was demonstrated that the development of CHB is strongly dependent on anti-SSA/Ro52 kDa.³ However, unknown environmental factors are also important.⁴ Based on clinical material from two countries the relative risk for developing CHB in children born of mothers/patients with primary Sjögren's syndrome (SS) was around 500 in both countries.^{5 6} CHB occurs spontaneously in one of 20 000 pregnancies.

Thus pathophysiological CHB and NLE are examples of passively acquired autoimmunity. However, CHB never develops after birth, in contrast with NLE which is self limiting, beginning on average 6 weeks after birth and lasting for 17 weeks (1.5–52) without reoccurrence. In contrast, CHB is a life threatening disease with increased morbidity and mortality even with pacemakers—for reviews see Tseng and Buyon⁷ and Lee.⁸

The purpose of this report is to describe:

anti-Sm, and anti-Scl-70 were normal/negative. Anti-SSA/Ro52, -60 kDa, and anti-SSB/La antibodies were positive, but negative 3 months later. The heart was found to be normal.

Evaluating the disease of the mother

When the fetal CHB was found an HEP-2 blood investigation of the mother showed positive ANA (titre 1/1024) with the presence of anti-SSA/Ro52, -Ro60, and anti-SB/La48 but not anti-DNA or anti-Scl-70 autoantibodies. She was referred to our Sjögren's Syndrome Research Centre. In April 2000 she still did not feel tired and denied symptoms from joints, eyes, mouth, and skin. However, she admitted that she had had irritation, gravel feelings, and photosensitivity in her eyes before becoming a teenager. She was used to these symptoms and thought they were "normal". She has never used eye drops or contact lenses. Objective tests for keratoconjunctivitis sicca (results in brackets)—Schirmer-I (4/5 mm/5 minutes), break up time (6/6 seconds), and van Bijsterveld score (4/5 units)—were abnormal. Objective tests for stomatitis sicca—unstimulated whole sialometry (0.4 ml/15 minutes), stimulated whole sialometry (4.0 ml/5 minutes), salivary gland scintigraphy (reduced uptake of isotope), lower lip biopsy (focus score >1/4 mm² glandular tissue)—were mostly abnormal. She fulfilled both the Copenhagen¹¹ and the European/US¹² classification criteria for Sjögren's syndrome.

DISCUSSION

The main aim of this report is to describe the unusual late start of NLE in a boy 20+1 weeks old. Several reviews have occurred in the past two decades and, to the best of our knowledge, NLE has always been reported to be present at birth,^{1 2 10} or to start at a mean of 6 weeks of age¹ and usually before week 13.^{2 10} The latest case previously described as being before week 20.¹

This report describes the two somewhat rare diseases—CHB and NLE—which form the basis for NLS in fetuses and newborn infants (CHB), and only observed post partum (NLE). Characteristically the NLS is seen in the offspring of mothers with primary SS.^{1 5 6 8}

NLE elements most often appear in the face but can become generalised and thus be located in non-sun exposed skin areas such as the back, in the groin, and on the soles of the feet. Mostly, mothers state that exposure to sunlight preceded the NLE elements by 1–2 days, as in this case. In contrast, patients with primary SS usually deny having skin photosensitivity, a striking difference from patients with systemic lupus erythematosus. The neonates have passively received IgG1 anti-SSA/Ro autoantibodies transplacentally and keep these autoantibodies for 24–32 weeks. Why the same autoantibodies sensitise the skin of the newborn but not of the mothers with primary SS remains to be explained. Photosensitivity, however, cannot be an important aetiological factor as NLE can be seen when the child is born and in non-sun exposed skin areas of the newborn.

The disappearance of the NLE elements in our case took place at the beginning of week 27, which was to be expected as the maternal IgG autoantibodies are metabolised after 24 (to 32) weeks. It should be emphasised that our case shows the spontaneous clinical course of the NLE as no glucocorticosteroids were used.

In more than 300 of our registered cases with premenopausal onset primary SS and the presence of circulating anti-SSA/B autoantibodies we have seen nine cases of CHB. Six of

these nine mothers were diagnosed with primary SS after the fetus/child had been diagnosed with CHB. The mothers in all cases denied having any complaints. However, they admitted their eyes were sensitive to light and they often drank water during the night. The objective tests for keratoconjunctivitis sicca and stomatitis sicca were (nearly) all very abnormal. The young patients with primary SS feel asymptomatic because their disease develops so early in life that they think that the usual SS complaints are "normal" as they have always felt this way.

Salomonsson *et al* found that the anti-Ro52 autoantibody was more important than anti-Ro60 for development of fetal CHB.³ The Australian mice studies suggest, however, that unknown local fetal milieu factors may be of greater importance than the anti-Ro52 autoantibody for development of fetal CHB.⁴ This might be valid even in man, but studies are lacking.

In conclusion, we have seen NLS in both children of a patient with primary SS—CHB in the first fetus and NLE when the second boy was 20+1 weeks old. This is the latest case of NLE so far described.

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