The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

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Neonatal lupus erythematosus

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1 Introduction

Neonatal lupus erythematosus (NLE) is a passively acquired, uncommon autoimmune disease, which is caused by the transplacental passage of maternal immunoglobulin G 52/60-kDa anti-Ro (SS-A) and/or 48-kDa anti-La (SS-B) autoantibodies or, less frequently, anti-U1 ribonucleoprotein (U1-RNP) autoantibodies [1, 2]. These antibodies have been found with high frequency in the sera of women with the rheumatic diseases, Sjögren's syndrome or systemic lupus erythematosus (SLE).

The pathogenesis of NLE probably involves more than simple transplacental passage of these antibodies, since the disease is rare, even in mothers who test positive for anti-Ro and anti-La antibodies. The incidence of NLE in children to mothers with SLE is about 1–2 %, and 15–20 % in children of mothers diagnosed with SLE and Ro antibodies, but also occurs in the children of asymptomatic women [3, 4]. NLE has been reported slightly more frequently in female than in male infants with an onset between birth and a few months of life [2].

The NLE syndrome is characterised most commonly by a transient lupus dermatitis or permanent congenital heart block (CHB). About 50 % of the NLE infants develop CHB, which carries a high mortality risk in the first year of life. The cardiac damage takes place between 18 and 24 weeks of gestational age [1]. During this period, the autoimmune reaction leads to an irreversible fibrotic destruction of the atrioventricular (AV) node in the foetus, which results in a low ventricular rate and, in the worst case, leads to a complete AV block and requires a permanent pacemaker implantation [1].

Skin lesions caused by NLE are present at birth or appear soon after and take the form of annular or circinate erythematous patches (Fig. 1), most often on the face and trunk [5]. Less frequently, NLE is associated with haematological and hepatic abnormalities, such as thrombocytopenia and an increased amount of transaminase enzymes. The noncardiac symptoms of NLE are transient and usually decline in parallel with the maternal antibody levels in the neonatal circulation within 2–6 months postpartum.

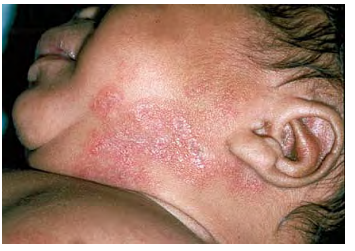

Figure 1. Erythematous patches and plaques on the face of a neonate with diagnosed NLE.

2 Diagnostic measurements for experts

Because of the potential for serious complications of undiagnosed NLE, a comprehensive evaluation of both child and mother is required and represents a unique challenge for rheumatologists, dermatologists, obstetricians, perinatologists, and paediatric cardiologists to identify pregnancies at risk and to care for the patients. In this context, neonatal and maternal serum should be tested for antinuclear antibodies (ANA), specifically for anti-Ro, anti-La antibodies, and anti-U1 ribonucleoprotein antibodies. Despite being positive for Ro and/or La antibodies, up to 60 % of infants' mothers with NLE may be clinically asymptomatic when their child develops NLE [5]. Mothers, in whom SLE is positively diagnosed by clinical symptoms and laboratory test results, should be monitored closely [2].

In addition to serum tests, a physical examination should be performed including a cardiac examination, an echocardiogram and electrocardiogram, liver function tests and a platelet count [5]. In women with autoimmune disorders, frequent ultrasonographic monitoring of the foetal heart rate is recommended during pregnancy [2]. The very early diagnosis of a foetal heart block by echocardiography is essential for appropriate therapy and the improvement of cardiac symptoms in the foetus [1].

In order to obtain an accurate diagnosis of NLE, skin biopsies for routine histology and direct immunofluorescence microscopy examinations are also recommended [2].

3 Requirements for family practitioners

Many women who bear a child with neonatal lupus syndrome have anti-Ro or anti-La autoantibodies, but do not have a diagnosis of lupus or another autoimmune disease at the time of their pregnancy. There is, however, a substantial risk of subsequent development of autoimmune connective tissue diseases [5].

Women with SLE should be referred to a rheumatologist and high-risk obstetrical provider to discuss their desire to have a child and to be informed about the

increased risk for the development of an autoimmune disease in their offspring before trying to become pregnant. The outcome for both mother and child is best when SLE has been under good control for at least six months before the onset of pregnancy. The patient should be regularly observed in order to provide timely prophylaxis. Furthermore, the development of the foetus must be monitored continuously during pregnancy. Postpartum, various examinations should be conducted by a neonatologist in order to confirm or to exclude the diagnosis NLE, which is generally based on clinical findings when maternal and/or neonatal autoantibody titres for anti-Ro (SS-A), anti-La (SS-B), and/or anti-U1-RNP are detected.

4 Follow up

Clinical observations

Children with NLE need continued follow-up visits, especially prior to adolescence and if the mother herself has an autoimmune disease. Although these children may not be at increased risk of developing SLE, the genesis of any type of autoimmune disease in early childhood may be of concern.

Patients with NLE and cardiac involvement require monitoring to assess the cardiac function and the necessity for a pacemaker. Mothers of neonates with NLE, particularly neonates with CHB, have a two- to three-fold increased risk of further affected neonates. An estimated 25 % of subsequent pregnancies are affected, and thus should be carefully monitored, particularly between 18 and 24 weeks of gestational age [6].

Expectations

The neonatal mortality rate of NLE patients with congestive heart failure is 20–30 %. Skin, haematologic and hepatic manifestations usually improve with the disappearance of maternal autoantibodies. In some cases, severe liver failure with a poor prognosis may occur.

5 Management

It is recommended that the management of NLE be commenced before or, at the latest, during pregnancy and that both the mother and the child be treated.

Treatment of the mother

In general, the management of NLE includes medical treatment of disease flares in mothers with SLE, who are at high risk of bearing an affected child, by using drugs that are effective against the disease but also safe for the foetus. Such an

approach may diminish or reduce the prevalence of the child developing complete heart block in association with NLE. In this context, corticosteroids and some immunosuppressive drugs are sometimes used, but long-term data in children exposed to immunosuppressive drugs *in utero* is lacking [2].

Treatment of the neonate

The treatment of the neonate must be individualised according to the manifestation of NLE, which consequently also affects the long-term prognosis of the child.

In patients with NLE that affects the heart, pacemaker placement along with the surgical correction of structural abnormalities in the heart may be necessary.

NLE that affects the skin, blood, spleen, or liver is usually self-limited and resolves without intervention within 2–6 months. In more severe cases, supportive treatment is possible for NLE skin lesions by using mild topical corticosteroids to control cutaneous lesions, antimalarial agents (e. g. hydroxychloroquine) to inhibit chemotaxis of eosinophils and locomotion of neutrophils and, possibly conducting laser treatment for residual telangiectasia. Additionally, photoprotection by avoiding direct sun exposure and applying sunscreens is highly desirable because solar exposure may precipitate skin lesions.

6 Diagnostic tests

NLE should be suspected in any infant born with CHB or who develops erythematous cutaneous patches and telangiectases. For the diagnosis of NLE various examinations are necessary. Commonly, antibodies to Ro (SS-A) and La (SS-B) are detected clinically by 'Ouchterlony' immunodiffusion, enzyme-linked immunosorbent assays (Elisa), or Western blot in both the infant and the mother. While the 'Ouchterlony' immunodiffusion test system is used as a screen for these antibodies without indicating their specificity, recombinant antigens have been created for the selective detection of the target antibodies in immunosorbent assays, which are much more sensitive and widely used especially to test for Ro52 antibodies. For a diagram of the indirect competitive Elisa method, using the example of Ro52, see Fig. 2: a buffered solution of recombinant Ro52 antigens is added to the microtitre plate, where they adhere via charge interactions (Fig. 2a), and the remaining free plastic surface is blocked with non-reacting proteins. In the next step, serum which may contain pathologic concentrations of Ro52 antibodies as well as an enzyme-linked competitive antibody is added (Fig. 2b). Both of them compete for binding with the coating antigen on the microtitre plate (Fig. 2c). After washing, the enzyme-linked secondary antibody is activated by adding a specific substrate causing a colour reaction that can be measured photometrically (Fig. 2d). The more intense the colour, the less antibody of interest is present in the serum sample.

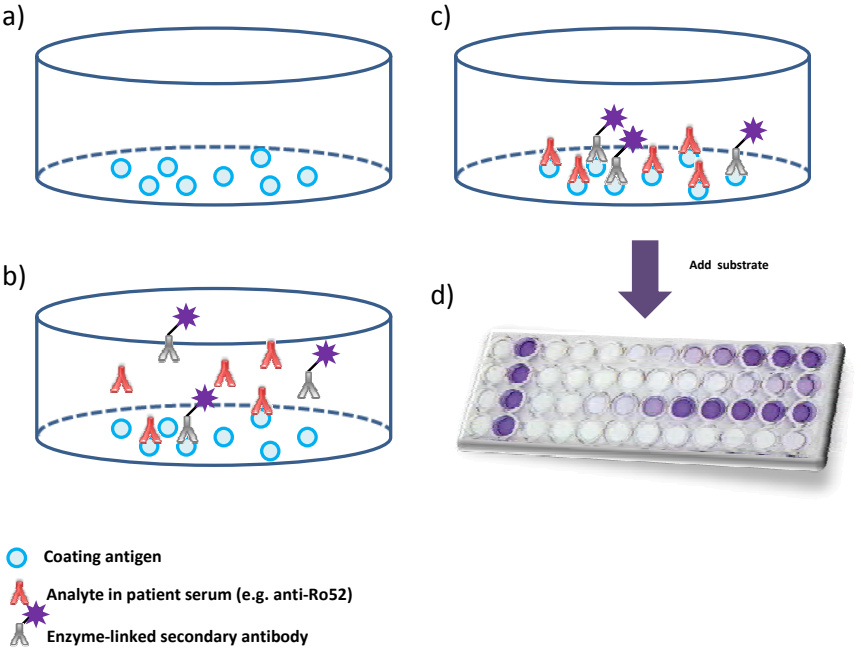

Figure 2. Schematic presentation of the indirect competitive Elisa method: a) coating antigen on microtitre plate, b) add serum with target antibody and enzyme-linked competitive antibody, c) competition for binding with the coating antigen d) microtitre plate after addition of activating substrate.

A third serological test used to diagnose NLE is called the immunoblot or Western blot. By means of this test it is possible to distinguish between antibodies to Ro52 and Ro60, as well as La and U1-RNP autoantibodies.

In order to confirm the diagnosis of NLE, especially when skin alterations appear, biopsies are examined histologically. Microscopic examination reveals hyperkeratosis in the affected areas, a thickened basement membrane, and a large number of CD4 T-lymphocytes. Furthermore, it may be useful to perform the Lupus band test by direct immunofluorescence staining to determine the presence and extent of immunoglobulin and complement deposits in skin biopsies from the affected tissue in comparison to non-lesional skin.

7 Testing methods

Several serological tests are available for the detection of autoantibodies specific for NLE. Differences appear in their specificity, sensitivity, and their intensity of

labour. 'Ouchterlony' immunodiffusion is generally being replaced by more sensitive enzyme-linked immunosorbent assays, while the Western blot exhibits a broad specificity but is very labour-intensive, and thus is primarily used for research studies. In general, all of these tests permit a safe diagnosis of NLE, especially when combined with the histological assessment of biopsied tissue samples.

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