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Report

Neonatal Lupus Erythematosus: Fifteen Cases Report and Review of Literature

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Abstract: Neonatal lupus erythematosus (NLE) is a rare autoimmune disease caused by the transplacental transfer of maternal autoantibodies, especially anti-Ro/SSA, anti-La/SSB, and anti-U1RNP. The objective of this study was to review the clinical, paraclinical, and therapeutic management of fifteen newborns admitted to a neonatal reanimation center at Children's Hospital A. Harouchi, Ibn Rochd University Hospital Centre. Results: Among these fifteen newborns, two categories were observed: the first category included eleven newborns of known lupus mothers in whom the electrocardiogram systematically requested came back normal. Skin lesions or biological abnormalities were found in some of these newborns, while others were completely asymptomatic. Simple clinical and paraclinical monitoring was performed, and the short- and long-term evolution was favorable. The second category included four newborns of mothers initially not known to have lupus but in whom the diagnosis of SLE was established after a maternal check-up because of neonatal bradycardia or suggestive skin lesions. In these four newborns, the systematic ECG revealed complete atrioventricular block in two and right bundle branch block in another. The cardiac ultrasound revealed cardiac malformations in three newborns. The systematic biological assessment showed abnormalities in two, and skin lesions were found in two newborns. In the cases of BAVc and BBD, the treatment consisted of pacemaker implantation, whereas simple monitoring was carried out in the newborn with cutaneous lesions. In conclusion, the clinical manifestations of NLE are varied; they may include temporary onset or irreversible symptoms such as congenital heart block (CHB), particularly third-degree heart block, which is the most serious complication of NLE because of its high morbidity and mortality rate and requires strict monitoring of all mothers with known lupus or with risk factors.

Keywords: Neonatal, Lupus Erythematosus, Autoantibody, Heart Block

1. Introduction

The neonatal lupus erythematosus (NLE) is a rare autoimmune disease, with an estimated incidence of 1 in 12,500 –20,000 in newborns [1]. It is caused by the transplacental transfer of maternal antinuclear antibodies (ANA) and extractable nuclear antigen antibodies (ENA) at the time the placenta is formed in the 12th week of pregnancy. [2]

The most incriminating ENAs in the pathogenesis of the NLE are anti-Ro/SSA, anti-La/SSB and, less frequently, anti-U1 ribonucleoprotein RNP. The diagnosis of neonatal lupus erythematosus needs a high index of suspicion and the absence of a family history makes it difficult; it relies on a combination of clinical and paraclinical findings. [3] The most common symptoms of Neonatal Lupus Erythematosus (NLE) are cutaneous rash, hematological, and hepatic abnormalities. They are temporary and disappear spontaneously over a period of time proportional to the decrease in antibodies in the fetal blood. Overall, 2% of children will develop irreversible symptoms [4], including the cardiac manifestations of neonatal lupus, which include complete atrioventricular block

or, in some cases, other lesions such as cardiomyopathy, and result in fetal death in one-fifth of cases requiring the implantation of a pacemaker for life in most surviving infants. [4] Only 50% of mothers have symptoms of connective tissue disease at the time of diagnosis, especially systemic lupus erythematosus (SLE) or Sjogren's syndrome. they may be completely asymptomatic at the time of childbirth. [5, 6] In Morocco, few studies have been published; for this reason, our paper outlines the clinical and paraclinical particularities, the therapeutic management, and the prognosis of fifteen newborns with NLE, relating them to other studies in the scientific literature in order to contribute to the improvement of the management of this pathology.

2. Patients and Methods

We retrospectively analyzed the medical records from the department of medicine and neonatology at the Ibn Rochd University Hospital Center in Casablanca, Morocco. Over a period of ten years, from January 2012 to December 2022.

This study included fifteen newborns, including two from twin pregnancies, hospitalized in the department of medicine and receiving neonatal resuscitation for neonatal lupus or having their mothers followed for systemic lupus erythematosus.

The inclusion criteria were bradycardia revealing maternal SLE or characteristic cutaneous lesions, and newborns from mothers were followed for systemic lupus erythematosus.

The diagnosis is usually established based on the clinical features and antibodies titres in the serum of the mother or the affected infant.

A full history and physical examination were accomplished, and laboratory testing, including liver function tests and a complete blood count, as well as the antibody titres and the determination of antibodies to SSA/Ro and SSB/La, were performed by the clinical immunology laboratory.

An electrocardiogram (ECG) was performed systematically for all the patients.

A telephone questionnaire was used to investigate the health status of the infants with NLE.

3. Results

A total of fifteen newborns were collected during the ten years (2012–2022) of our study, they were male in eight cases (53%), and female in seven cases (46%), the sex ratio was 1.2.

Most of the newborns were full term. According to the FARR score, the gestational age was less than 37 weeks in six newborns, between 37 and 41 weeks + 06 days in seven newborns, and greater than or equal to 42 weeks in two newborns.

(1) The main manifestations in affected children

Various manifestations were reported, including cardiac, cutaneous, hematological, hepatobiliary and neurological.

1) Cutaneous manifestations

Among fifteen newborns, five (33,3%) have cutaneous manifestations; the rash was present in four patients at birth and one after three days. One newborn had erythematopapular lesions on the palpebral region, the trunk, and the legs; one had macular and erythematous lesions on the forehead and bilaterally in the palpebral area; one had slightly erythematous atrophic lesions on the face and scalp as well as a periorbital inflammatory erythema; one had maculo-pustular lesions on the face; and one infant had scaling of the abdomen and limbs. All the patients were advised to avoid the sun, and none of them had to take a prescription for medication.

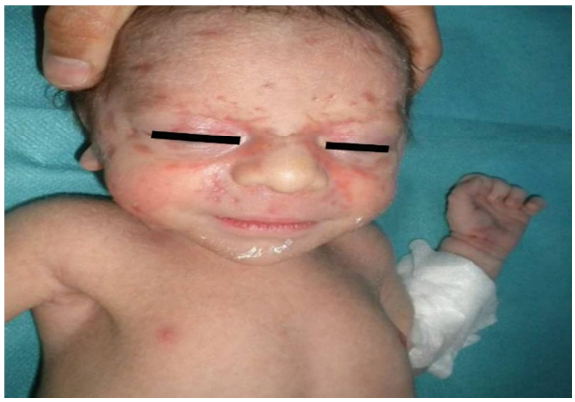

Figure 1. *Periorbital inflammatory erythematous.*

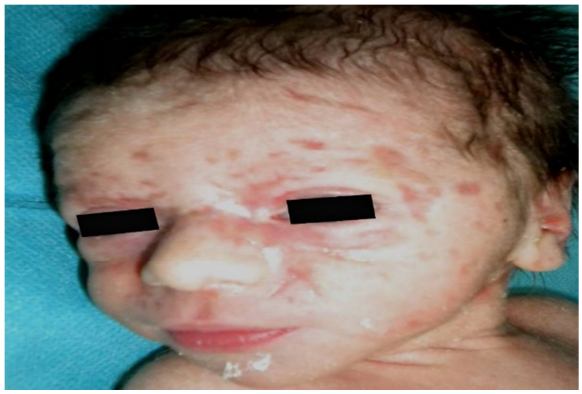

Figure 2. *Atrophic lesions on the face and scalp and periorbital inflammatory erythematous.*

2) Cardiac manifestations

Three newborns had bradycardia on clinical examination, and one had a heart murmur.

A systematic ECG was performed in all our patients at birth; it revealed a complete atrioventricular block in two newborns (One of whom was first detected in utero during a routine ultrasound performed at 26SA), and an isolated right bundle branch block in one newborn. All of these newborns are from mothers not initially known to have lupus at the time of diagnosis.

A cardiac ultrasound revealed interventricular communication in two newborns at seven and eight days of life, respectively. A persistent ductus arteriosus in two newborns, diagnosed at three and seven days of life, respectively; an interatrial communication in another neonate, diagnosed at seven days of life, and two cases of complete atrioventricular block were found.

The indication for pacemaker implantation was given and

performed in both cases with complete atrioventricular at 11 months and 30 months of age, with good evolution. Patients with cardiac malformations were referred to the cardiovascular surgery department for follow-up and management. In the other forms, a simple monitoring system was set up.

3) Hematological manifestations

All newborns had a blood count on admission and regularly during their hospitalization, hematological abnormalities were seen in five patients (33,3%).

The median age of onset of hematological manifestations was one day, with extremes ranging from one to three days. These comprised isolated anemia in one newborn, isolated thrombocytopenia in the second twin, isolated lymphopenia in a newborn who subsequently developed anemia twelve days later, and lymphopenia associated with thrombocytopenia in two newborns.

Thus, a total of three of the neonates with hematological findings had abnormalities in two blood lines simultaneously.

4) Hepatobiliary manifestations

A cytolysis was discovered at H24 of life in one newborn (6,66%).

5) Antibodies prevalence.

Most cases of NLE showed anti-SS-A/Ro antibodies, anti-SS-B/La antibodies, or both.

Anti-SS-A/Ro antibody alone was seen in ten cases (66.6%), anti-SS-B/La antibody alone in six cases (40%), both anti-SS-A/Ro and anti-SS-B/La antibodies in six cases (40%).

6) Evolution

The median length of hospitalization was 5.5 days, with extremes of 2 to 33 days. Evolution was assessed by clinical, biological and radiological data. Short-term outcome was favorable for all newborns.

(2) Clinical characteristics of the mothers

Table 1. *The immunological profile of the newborns in our study.*

	Maternal background	Newborns	Antibodies		
			AAN	Anti-SSA	Anti-SSB
Presenting symptoms of neonatal lupus	Not known to have lupus (CHB)	1	+	+	-
	Not known to have lupus (CHB)	2	+	+	+
	Not known to have lupus	3	+	+	+
	Not known to have lupus	4	+	+	+
	known to have lupus	5	+	+	+
	known to have lupus	6	+	+	-
	known to have lupus	7	+	+	-
	known to have lupus	8	+	+	-
	known to have lupus	9	+	-	-
	known to have lupus	10	+	+	+
Asymptomatic	known to have lupus	11	+	-	-
	known to have lupus	12	+	-	-
	known to have lupus	13	+	-	-
	known to have lupus	14	+	-	-
	known to have lupus	15	+	+	+

Among the fifteen mothers in our study, ten (66%) were known to have lupus, two of whom also had antiphospholipid antibody syndrome (APAS), and they were all followed at the internal medicine department of Ibn Rochd University Hospital Center. Among these mothers, two were receiving corticosteroids (prednisolone), one mother was treated with a combination of corticosteroids (prednisolone) and azathioprine (ATP), one mother was receiving hydroxychloroquine (HCQ), three were on a combination of hydroxychloroquine and prednisolone, and two were on a combination of hydroxychloroquine and corticosteroids (prednisolone) and azathioprine (ATP). The median duration of a diagnosis of lupus was three years. Five mothers (50%) presented a flare during their pregnancy. Three mothers (30%) had stage IV lupus nephropathy, and two had a hematological and articular relapse. However, four mothers (26%) were not initially known to have lupus at the time of delivery.

4. Discussion

Neonatal lupus erythematosus (NLE) is a rare autoimmune disease that is an example of passively acquired autoimmunity.

It can be defined as a set of clinical symptoms and signs resulting from the passage of maternal autoantibodies (most commonly anti-Ro/SSA and anti-La/SSB, and rarely anti-U1RNP) across the placenta. [7]

Environmental factors and fetal genetics also play a role in pathogenesis, which makes some children sensitive to the presence of these maternal autoantibodies. [1-8]

The true incidence has not yet been defined due to underdiagnosis and misdiagnosis. However, it affects approximately 1 in 12,500 to 20,000 newborns and can affect all ethnic groups, with female predominance. Our study found a male predominance. [1]

At the time of diagnosis, approximately half of the mothers are asymptomatic and have only positive anti-Ro2 antibodies. Importantly, the healthy mothers of these children are at high risk of developing connective tissue disease in the future with a 20% chance of recurrence in three consecutive pregnancies. [5, 6]

The clinical picture of the disease is multiform; the symptoms can be temporary (for example skin lesions) or include organ changes such as hematological, hepatological, or irreversible disorders, such as congenital heart block. (CHB). [4] Cardiac symptoms are less common and

disappear during the first few months of life, coinciding with the disappearance of maternal serum antibodies.

In a recent study of 17 patients with NLE, cutaneous, cardiac, hepatobiliary, and hematologic involvement were observed in 71%, 65%, 53%, and 35% of infants, respectively. [6]

In our study, the cutaneous involvement was of the same frequency as the cardiac and hematological manifestations, then neurological and hepatobiliary.

The cardiologic complications of neonatal lupus may include first-, second-, and third-degree atrioventricular block, fibroelastosis of the endocardium, dilated cardiomyopathy and transient arrhythmias.

Atrioventricular block is the most common and serious cardiac complication of neonatal lupus because it is irreversible and carries high morbidity and mortality, especially third-degree heart block, which requires pacemaker implantation. [4]

Most cases are diagnosed between 18 to 24 weeks of age, which corresponds to the first prenatal ultrasound. Tunaoglu, Yildirim, and Vurali pointed out that this period corresponds to the time of transfer of the maternal IgG antibodies to the fetus, especially anti-Ro/SSA antibodies that are involved in the development of NLE with complete heart block. [9]

The risk of CHB is higher in the population of anti-SSA-positive mothers, reaching 1% to 2% if the child from the first or previous pregnancy does not have neonatal lupus, but older siblings do not have the disease. Increased risk of 10-20%. [10-13]

A variety of treatments may be used, including corticosteroid therapy, intravenous immunoglobulin, and plasmapheresis. [4]

Studies by Sonesson et al. On a group of 212 patients showed that fluoride steroids can reverse first- and second-degree atrioventricular block, but also that third-degree atrioventricular block can be reversible if treatment is started soon after its onset [14].

Another study shows that prenatal maintenance therapy with prednisolone or betamethasone given to the mother early in pregnancy (before 16 weeks' gestation) may reduce the risk of developing antibody-mediated congenital heart block in the child. [15]

In our study, cardiac lesions were observed mainly in patients whose mothers were not known to have lupus and therefore had not received prior treatment, which is in agreement with studies conducted on the important role of corticosteroid therapy in reducing the risk of cardiac manifestations in NLE.

Regarding, intravenous immunoglobulin early use after detection of atrioventricular block may increase the chance of recovery of sinus rhythm. [4]

Cutaneous findings may be present at birth but often appear in the first few weeks of life, sometimes after sun exposure or phototherapy.

Exposure to anti-SS-B antibodies and female gender are risk factors for the development of skin lesions. [4]

Ring-shaped erythematous or polycystic plaque with or without scars characterizes NLE and appears mainly on the scalp, neck, or face probably because these are exposed areas. Periorbital erythema, referred to as ‘the eye of the raccoon’ or ‘the eye of the owl’, is a common feature. [4] In addition to typical lesions, lesions resembling seborrheic eczema or a fungal infection may also be seen. [16]

Histologically, the lesions are similar to those of subacute lupus with hyperkeratosis, epidermal atrophy, basal degeneration, intracellular oedema, and perivascular infiltrations by inflammatory cells. In addition, direct immunofluorescence reveals complement and immunoglobulin complexes. [4]

They tend to resolve spontaneously without a scar, but hypopigmentation or hyperpigmentation may sometimes persist, and disappear within a few months after birth.

Therapeutic approach consists mainly of photoprotection and low-dose topical corticosteroids.

In addition to cardiac and cutaneous manifestations, other onset may be observed such as hepatic, hematological, central nervous system involvement.

Anemia, neutropenia and transient thrombocytopenia have been observed; however, no lymphopenia has been observed in LN patients. These hematological manifestations usually disappear in 2 to 3 months without treatment [17-19].

For liver damage, it can cause elevated transaminases, direct hyperbilirubinemia, cholestatic hepatitis and fulminant liver failure, the latter of which can occur in utero or after birth. [18]

In addition to the clinical features described above, the presence of autoantibodies in the maternal or fetal serum is crucial to confirm the diagnosis of NLE.

Moreover, once the diagnosis of NLE is confirmed, all the newborns must be followed up regularly for the subsequent development of autoimmune diseases.

5. Conclusion

We conclude that the polymorphic presentation of NLE necessitates increased follow-up of these patients in rheumatology, dermatology, and possibly cardiology. Pregnant women with known lupus should be monitored, and their therapy must be adjusted. In asymptomatic cases, risk factors such as a history of a child with neonatal lupus or elevated anti-Ro titers should be investigated at the earliest sign of systematic lupus, especially in the frustrated forms, before the onset of irreversible fetal symptoms, including CHB.

Conflicts of Interest

The authors declare no conflicts of interest.

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