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ORIGINAL RESEARCH ARTICLE

Prevalence of neonatal lupus in a small group of antibody-carrying mothers and frequency of complete atrioventricular block

Prevalencia de lupus neonatal en un pequeño grupo de madres portadoras de anticuerpos y frecuencia de bloqueo auriculoventricular completo

Héctor González-Zambrano[1,2], Gerardo Orozco-Barocio[3], and María C. Franco-Ramos[4]*

[1]Cardiology Service, Hospital General de Occidente, Ministry of Health; [2]National Institutes of Health, Ministry of Health; [3]Rheumatology Service, Hospital General de Occidente, Ministry of Health; [4]State Public Health Laboratory. Jalisco, México

Abstract

Background: *Neonatal lupus (NL) is extremely rare and is caused by the transplacental passage of maternal IgG autoantibodies against Ro, La, and/or RNP proteins into the fetal circulation, which can cause congenital complete atrioventricular block (CCAB), permanent skin lesions, and liver involvement.* **Objective:** *To know the prevalence of NL in patients with CCAB and the clinical course in long-term follow-up.* **Methods:** *From January 1992 to December 2017, patients with CCAB were included. The presence of anti-SSA/Ro and anti-SSB/La antinuclear antibodies in maternal serum confirmed NL.* **Results:** *Eight patients were included with a follow-up of 10 ± 6 years; NL was concluded in 62.5%; two were male. One of them was diagnosed in utero, two at birth, and a pacemaker was implanted in them, one at 12 years of age and another at 15. The other two cases were diagnosed at 18 and 26 years of age, and permanent pacemakers were implanted 8 and 5 years later, respectively. In one case, a definitive pacemaker was not implanted in a newborn with only 1 year of follow-up. At delivery, 60% of the mothers were free of rheumatic disease, and altogether, they all had 19 children; none of them presented NL manifestations.* **Conclusions:** *CCAB is rare and frequently associated with a maternal autoimmune disease, practically all of them will require a definitive pacemaker at some point in their lives.*

Keywords: *Neonatal lupus. Congenital complete atrioventricular block. Systemic lupus erythematosus. Sjogren's syndrome.*

Resumen

Antecedentes: *El lupus neonatal (LN) es extremadamente raro y es ocasionado por el paso transplacentario de auto-anticuerpos maternos IgG contra las proteínas Ro, La y/o RNP a la circulación fetal que puede ocasionar bloqueo aurículo-ventricular completo congénito (BAVCC) permanente, lesiones dérmicas y afectación hepática.* **Objetivo:** *Conocer la prevalencia de LN en paciente con BAVCC y la evolución clínica en un seguimiento a largo plazo.* **Métodos:** *De enero de 1992 a diciembre 2017 se incluyeron paciente con BAVCC. La presencia de anticuerpos antinucleares anti-SSA/Ro y anti-SSB/La en suero materno confirmó LN.* **Resultados:** *Ocho pacientes fueron incluidos con seguimiento de 10 ± 6 años, el 62.5 % con LN; dos fueron del sexo masculino. Uno diagnosticado in útero, dos al nacimiento, en ellos se implantó marcapaso; uno a los 12 años*

***Correspondence:**
Héctor González-Zambrano
E-mail: hector.gz@hotmail.com

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de edad y otro a los 15. Los otros dos casos fueron diagnosticados a los 18 y 26 años, se implantó marcapaso definitivo en ellos 8 y 5 años después respectivamente. En un caso no se implantó marcapaso definitivo; un recién nacido con solo un año de seguimiento. Al dar a luz, el 60 % de las madres estaban libres de enfermedad reumática y en conjunto todas tuvieron 19 hijos, ninguno de ellos presentó manifestaciones de LN. **Conclusiones***: El BAVCC es raro y frecuentemente está asociado a una enfermedad autoinmune materna, prácticamente todos requerirán de marcapaso definitivo en alguna época de su vida.*

Palabras clave: *Lupus neonatal. Bloqueo auriculoventricular completo congénito. Lupus eritematoso sistémico. Síndrome de Sjögren.*

Introduction

Neonatal lupus (NL) is an extremely rare autoimmune disease, with an estimated incidence of 1 in 20,000 live newborns. It occurs due to the transplacental passage of maternal IgG autoantibodies anti-Ro/SSA, anti-La/SSB, and very rarely anti-U1RNP[1,2]. The mothers are usually carriers of a connective tissue disease, mainly sjögren's syndrome (SS) or systemic lupus erythematosus (SLE), although around 50% may be asymptomatic at the time of delivery. The condition is characterized by transient and permanent alterations; within the transient ones, dermatological involvement is primarily found, but hepatic[3], hematological[4], central nervous system[5], and even pulmonary[6] manifestations are also mentioned. Third-degree atrioventricular block is a permanent manifestation; the deposition of maternal anti-Ro/SSA antibodies can cause inflammation, fibrosis, and calcification in the conduction system and on the atrioventricular node, and this seems to be responsible for heart block. Other structural heart abnormalities have also been reported[7]. In some newborns of mothers with anti-SSA/Ro and anti-SSB/La autoantibodies, heart block is not present at birth, but it has been postulated that it may develop at some point in childhood. It is not always complete, and its degree can increase over time until it becomes congenital complete atrioventricular block (CCAB)[8]. The main objective was to determine the prevalence of NL in patients with CCAB and its long-term evolution in a tertiary care hospital.

Methods

From January 1993 to December 2018, all patients with a diagnosis of CCAB referred to the cardiology department were included, regardless of their age at presentation. The diagnostic criteria of CCAB in adult life proposed by Yater[9,10] were applied, and the electrocardiographic criteria used were: the atria and ventricles should be completely dissociated, the ventricular rate should be slower than the atrial rate, and no captured beats should be present. Cases in which it was not possible to search for anti-SSA/Ro and anti-SSB/La antibodies in the patients' mothers were excluded. The diagnosis of NL was made by finding maternal antinuclear antibodies, either anti-SSA/Ro and/or anti-SSB/La. The positive cases underwent long-term clinical follow-up to determine their evolution and the moment of permanent pacemaker implantation. 24-h Holter was performed several times during the course of the follow-up, and according to the clinical evolution, an echocardiogram was also performed to search for other cardiological abnormalities. The mothers underwent a complete medical history and laboratory tests, including a blood count, blood chemistry, liver function tests, and anti-SSA/Ro and anti-SSB/La antibodies. In addition, specialized immunological tests are needed in cases of clinical suspicion of collagen disease. The possible existence of another child with NL involvement was also investigated.

Results

Ten cases with CCAB were referred to the cardiology service; only eight were included since maternal anti-SSA/Ro and anti-SSB/La antibodies were not determined in two of them. Table 1 describes the clinical characteristics of the cases included in CCAB. In 5 (62.5%) cases, NL was confirmed by the detection of antinuclear antibodies in the mothers of the patients. They underwent a clinical follow-up that ranged between 13 and 219 months with an average of 124 ± 69 months; three were male and two were female; all were full-term infants and were asymptomatic at the time of their first review; none had heart failure; and none died during the follow-up. In one, CCAB was diagnosed at 33 weeks of gestation, and in another two at birth. In the patient diagnosed in the gestational stage and another diagnosed at birth, patent ductus arteriosus was detected, which was surgically corrected at 12 months of age in both. None of the three newborns with NL presented dermatological or other types of involvement during the

Table 1. Baseline characteristics of patients with congenital complete atrioventricular block

Case No.	Age (years)	Sex	Age at pacemaker implantation (years)	Congenital heart disease	Clinical follow-up (months)	Extracardiac manifestations of NL	Neonatal lupus confirmation*
1	27	F	29	No	30	No	Rejected
2	33gw	M	12	PDA	150	No	Confirmed
3	NB	M	15	PDA	219	No	Confirmed
4	9	F	10	ASD	15	No	Rejected
5	26	F	31	No	89	No	Confirmed
6	18	F	26	No	148	No	Confirmed
7	29	M	40	No	170	No	Rejected
8	NB	M	NRY	No	13	No	Confirmed

*Confirmed by positive maternal antibodies anti-Ro/SSA and/or anti-La/SSB.
ASD: atrial septal defect; Dx: diagnosis; gw: gestation weeks; NB: newborn; NL: neonatal lupus; NRY: no required yet; PDA: patent ductus arteriosus.

neonatal stage. The other two cases were diagnosed at 18 and 26 years of age; the mothers of these patients denied evidence of skin lesions in their children before 6 months of age compatible with NL, and no congenital heart disease was detected in them. Of the five cases with NL, four (80%) required definitive pacemaker implantation due to bradycardia of < 55 beats/min and manifestations of low cerebral blood flow, with an average age at the time of pacemaker implantation of 21 ± 8 years. The mothers of the positive cases had an average age at the time of giving birth of 29 ± 5 years (Table 2), and 3 (60%) were free from rheumatologic symptoms. At the end of follow-up, in four, a collagen disease was diagnosed; one already had a diagnosis of SS, and another had reported rheumatic symptoms for the previous 4 years but had not attended a specialized rheumatology clinic. However, when she was studied at the birth of her son, SLE was concluded. The two mothers with children detected in the late stage manifested the onset of rheumatic symptoms 10 and 14 years after the birth of their children, and SS was demonstrated in both. Altogether, the five mothers had a total of 19 children; none of their other children were diagnosed with NL. As we can see in table 2, all mothers had positive anti-SSA/Ro antibodies, with values > 50 U/mL (72.4 ± 6.37 U/mL), but only two had anti-SSB/La antibodies.

Discussion

To our knowledge, this is the first report in our country where the prevalence of NL in patients with CCAB is studied, since, in our population, there is only one study where a follow-up of 93.7 + 104 months is carried out in 67 patients with CCAB; however, the association of CCAB with NL was not studied[11], and even though our study sample is small, there are many similarities with the findings published in the medical literature.

In this study, we adopted the definition of *bloqueo aurículo-ventricular completo congénito* proposed by Yater[9,10], which has persisted through time and is still generally accepted: heart block is established in a young patient. However, there is a proposal to modify an atrioventricular block as congenital if it is diagnosed in utero, at birth, or within the neonatal period. Therefore, it has also been proposed that childhood atrioventricular block is diagnosed between the 1st month and the 18th year of life[12,13].

The most relevant transient manifestation in NL is dermatological involvement, which has a gender preference with a female-male ratio of 2:1 or 3:1[14]. Cardiological involvement does not have a defined gender predisposition. Dermatological lesions usually appear in the 1st weeks of life, generally after sun exposure. They tend to resolve spontaneously after 6 months of life, caused by the clearance of maternal antibodies in the infant, and usually do not leave a scar, although occasionally residual hypopigmentation or hyperpigmentation may appear that resolves in months or years. Dermatological lesions occur in isolation in approximately 50% of NL cases; cardiological involvement is found as the only manifestation in approximately 50% of patients; and both are present in 10% of those affected[15]. In our series of cases with NL, no

Table 2. Baseline characteristics of mothers with carrier children of congenital complete atrioventricular block

Case No.	Age at delivery	Anti SSA/ Ro	Anti SSB/ La	Previous diagnosis of rheumatic disease	Rheumatic disease at the end of follow-up	Total children	Another child with NL
1	23	(-)	(-)	No	No	5	No.
2	26	(+)	(+)	SS	SS	2	No.
3	29	(+)	(+)	SLE	SLE	2	No.
4	27	(-)	(-)	No	No	3	No.
5	28	(+)	(-)	No	SS	6	No.
6	39	(+)	(-)	No	SS	7	No.
7	31	(-)	(-)	No	No	4	No.
8	24	(+)	(-)	No	No	2	No.

(+): positive; (-): negative; SLE: systemic lupus erythematosus; SS: Sjogren's syndrome; NL: neonatal lupus.

dermatological manifestations were documented. The main risk factor for developing cardiological manifestations in the NL is the presence of maternal anti-SSA/Ro antibodies, especially when the levels are very high (> 50 U/mL)[16]. Although it is clear that it is not the only factor, these damages include transient intrauterine first-degree heart block, corrected QT interval prolongation, sinus bradycardia, dilated cardiomyopathy, endomyocardial fibroelastosis, hydrops fetalis[17-24], and some congenital heart diseases[25], such as atrial and ventricular septal defects, patent ductus arteriosus, coarctation of the aorta, and hypoplastic right ventricle. It has been documented that in the children of mothers carrying anti-Ro and anti-la antibodies, there is a possibility of an increased risk of developing not only CCAB but also Wolff-Parkinson White syndrome[26-29].

In this study, 100% of the mothers of the cases with NL were carriers of anti-SSA/Ro antibodies (levels > 50 U/mL), and only two were also found to have anti-SSB/La antibodies. The children of these two mothers were carriers of patent ductus arteriosus, which was the only associated heart disease in our cases.

Histologically, the lesion is characterized by fibrosis of the atrioventricular node, with the possibility of spreading to the myocardium and endocardium. This favors the appearance of endomyocardial fibroleastosis and dilated cardiomyopathy, significantly increasing morbidity and mortality due to heart failure[30,31]. In the long-term follow-up of our cases, no dilated cardiomyopathy, heart failure, or death occurred in any of them. On the other hand, atrioventricular block is generally complete and permanent, but it has been observed that it can be first- or second-degree and this could progress to complete atrioventricular block even in the postnatal stage, manifesting late. Therefore, it has been suggested to perform an electrocardiogram in children with mothers who are carriers of anti-SSA/Ro and anti-SSB/La antibodies during their development and growth[32,33]. In our study, CCAB was found in two patients at 18 and 26 years of age; both cases were female and had no cardiological symptoms, so there is a possibility that they did not present CCAB at birth and that it manifested at some stage during its late development. In both cases, a permanent pacemaker was implanted later when they presented clinical manifestations of low cerebral output with a heart rate of < 50 beats/min; this was at 26 and 31 years of age, respectively. On the other hand, their development and growth were completely normal. In congenital CCAB, the indication for a pacemaker will be related to the chronotropic response and the presence of alterations in growth and development; internationally, it has been postulated as follows: third-degree atrio-ventricular block in the infant with a ventricular rate < 55 beats/min or with cardiac heart disease and a ventricular rate < 70 beats/min, and third-degree atrio-ventricular block beyond the 1st year of life with an average heart rate < 55 beats/min[13].

It has also been shown that 40-60% of the mothers of these infants are asymptomatic at the time of the birth of their children and that they will later develop symptoms of some connective tissue disease[34]. We found that 60% of the mothers were asymptomatic when giving birth, but over time, 80% presented some connective tissue disease. The observation that not all infants with maternal anti-Ro/SSA and anti-SSB

antibodies will develop NL suggests that there are other factors that may contribute to the pathogenesis of this disease. Within the intrinsic factors, genetic factors, HLA susceptibility, and genetic defects of complement C4 and T receptors are mentioned; thus, extrinsic factors are also mentioned, such as an intrauterine viral infection, among others[35-37]. It has been reported that the risk of cardiological involvement in children of anti-Ro-positive mothers is 1-2%[38], and the recurrence of a second child with NL is 12-25%[39,40]. The five mothers in this investigation had a total of 19 children, and no evidence of NL was documented in any of their other children.

Conclusions

Although NL is very rare, the takeaway message from this research is that we should suspect this diagnosis in all patients with intrauterine bradycardia, hydrops fetalis, or CCAB, even when the mothers are free of rheumatic symptoms. The diagnosis of NL should also be suspected in young patients born to mothers with rheumatic disease with detection of heart block of any degree in the late phase, and the possibility that 1st or 2nd heart block may progress to CCAB should be considered and require a permanent pacemaker at some point in life. When patients with NL only present CCAB, the prognosis is usually very favorable in their development and growth.

Limitations

The main limitation of this study is that the study population consists of very few patients; therefore, the conclusions expressed in this document can be quite questionable. However, we found great similarity in the results of other studies with large samples. On the other hand, we think that the long follow-up carried out in this research offers a great contribution to the prognosis of patients with CCAB secondary to NL. We did not find the morbidity and mortality rates reported by other authors. We consider that it would be convenient to make a registry of the hospitals in the country where there are similar patients to prepare a joint report and, in this way, have more solid conclusions in this aspect of our environment.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appears in this article.

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