Review

Anti-SSA/Ro antibodies and the heart: more than complete congenital heart block? A review of electrocardiographic and myocardial abnormalities and of treatment options

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Abstract

Apart from complete and incomplete congenital heart block (CHB), new cardiac manifestations related to anti-SSA/Ro antibodies have been reported in children born to mothers bearing these antibodies. These manifestations include transient fetal first-degree heart block, prolongation of corrected QT (QTc) interval, sinus bradycardia, late-onset cardiomyopathy, endocardial fibroelastosis and cardiac malformations. Anti-SSA/Ro antibodies are not considered pathogenic to the adult heart, but a prolongation of the QTc interval has recently been reported in adult patients and is still a matter of debate. Treatment of CHB is not well established and needs to be assessed carefully. The risks and benefits of prenatal fluorinated steroids are discussed.

Introduction

Anti-SSA/Ro antibodies have long been associated with an increased risk of fetal congenital heart block (CHB). Apart from complete and incomplete CHB, new cardiac manifestations related to anti-SSA/Ro antibodies have been reported in children born to mothers bearing these antibodies. These manifestations include transient fetal first-degree heart block [1], prolongation of corrected QT (QTc) interval [2,3], sinus bradycardia [4], late-onset cardiomyopathy [5], endocardial fibroelastosis (EFE) [6,7] and cardiac malformation [8]. Classically, anti-SSA/Ro antibodies have not been considered pathogenic to the adult heart, but a prolongation of the QTc interval has recently been reported [9].

Electrocardiogram abnormalities and anti-SSA/Ro antibodies

Congenital heart block

Mothers known to have anti-SSA/Ro and/or anti-SSB/La antibodies are at risk for delivering an infant with neonatal lupus erythematosus syndrome, which is characterized by transient lupus dermatitis, hepatic and haematological abnormalities, and/or isolated CHB [10]. Skin rash, hepatitis and thrombocytopenia generally resolve without sequel. By contrast, the heart block is permanent and requires a pacemaker in about 66% of cases [10]. The mortality of CHB, which is predominant *in utero* and in the first months of life, is estimated at 16 to 19% [10–12]. When anti-SSA/Ro antibodies are present in sera of mothers with connective tissue diseases (CTD), the incidence of CHB has been reported to be 1 to 2% in live births [4,8]. The risk of recurrence of CHB in a subsequent child remains limited to 10 to 16% [10–12].

CHBs are usually complete but CHB of the first or second degree can also be observed. In Buyon's registry [13], 9 of 187 children with CHB had a first-degree block discovered at birth through systematic electrocardiogram (ECG). The block progressed after birth in four of these children. Four other newborn infants had a second-degree block; in two of them it progressed towards a third-degree block. Such postnatal progression of CHB has been described by others [12] and justifies performing ECGs in newborn infants born to anti-SSA/Ro-positive mothers even when the heart rate is normal.

Expansion of the spectrum of conducting abnormalities

In 2000, Glickstein and colleagues [14] developed pulsed Doppler-derived PR interval measurements in fetuses, to identify a first-degree block *in utero*. The method consists of measuring the time interval from the onset of the mitral A wave (atrial systole) to the onset of the aortic pulsed Doppler tracing (ventricular systole) within the same left

CHB = congenital heart block; CTD = connective tissue diseases; ECG = electrocardiogram; EFE = endocardial fibroelastosis; PRIDE = PR interval and dexamethasone evaluation in CHB; QTc = corrected QT.

ventricular cardiac cycle. These authors recently validated the accuracy of this method among physicians participating in a multi-centre prospective fetal echocardiographic study [15]. Using the same method, Sonesson and colleagues [1] prospectively investigated the development of heart block in 24 unselected fetuses of anti-SSA/Ro positive mothers. Results were compared with a large control population of 284 healthy fetuses (data about 264 of these fetuses had previously been published [16]). A first-degree block was detected in eight fetuses between 18 and 24 weeks of gestation. One of these eight fetuses had progression to complete CHB despite treatment with betamethasone, whereas another that had progressed to a second-degree block improved to a first-degree block after treatment with betamethasone. In the remaining six fetuses, first-degree blocks were transient, and spontaneous recovery occurred before or shortly after birth [1].

The same issue was investigated in a prospective multicentre study named PRIDE (PR interval and dexamethasone evaluation in CHB). This study is continuing and assesses weekly the mechanical PR interval in pregnant women with anti-SSA/Ro and/or anti-SSB/La antibodies. Preliminary results [17] did not confirm the high frequency of transient fetal first-degree CHB found by Sonesson and colleagues [1]: only two first-degree CHBs were observed in 66 enrolled pregnant women. Discrepancies between these results might be related to technical differences in measurements of PR as discussed during the Fourth International Conference on Sex Hormones Pregnancy and the Rheumatic Diseases (Stresa, September 2004), and further studies are needed to clarify this point.

QTc interval prolongation in children

In the absence of CHB, a prolongation of the mean QTc interval has been reported by Cimaz and colleagues [2] in 21 children born to anti-SSA/Ro-positive mothers in comparison with 7 infants born to anti-SSA/Ro-negative mothers with CTD. QTc prolongation resolved during the first year of life [18]. Similar results were found by others [3]. However, we have recently addressed the same issue in a study that compared ECGs in 58 consecutive children aged 0 to 2 months born to anti-SSA/Ro-positive mothers with a carefully defined control group of 85 infants aged 0 to 2 months born to anti-SSA/Ro-negative mothers with CTD. No difference was found for QTc, PR and heart rate, and this remained true at 2 to 4 months of life [8]. Interestingly, the mean QTc interval recorded during the period from 2 to 4 months showed a significant lengthening in comparison with those obtained during the period from 0 to 2 months in both anti-SSA/Ro-positive and anti-SSA/Ro-negative groups. In agreement with this, in a prospective study of 4,205 healthy newborn infants, Schwartz and colleagues [19] have shown that there was a physiological lengthening of the QTc interval at the second month of life. This might explain why Cimaz and colleagues [2] found a prolongation of QTc in the anti-SSA/Ro-positive group: at ECG recording, the median age of this group was 90 days, compared with 7 days for the anti-SSA/Ro-negative controls. The data are summarized in Table 1.

QTc interval prolongation in adults

Until recently, it was supposed that CHB is due to a peculiar vulnerability of the fetal heart between 16 and 30 weeks of gestation, and anti-SSA/Ro antibodies were not considered pathogenic for the adult heart. In support of this, Gordon and colleagues [20] did not find abnormalities of PR, QRS or QTc in ECGs of adults with anti-SSA/Ro antibodies. Recently, Lazzerini and colleagues [9] reported a significant prolongation of the mean QTc interval in adult patients with anti-SSA/Ro-positive CTD in comparison with the controls (anti-SSA/Ro-negative CTD) [9]. However, in our study of 89 ECGs of adults with CTD, there was no difference in QTc interval between the two groups [21]. Thus, in agreement with Gordon and colleagues [20], we think it unlikely that the presence of anti-SSA/Ro antibodies is associated with prolongation of the QTc interval in adult patients with CTD. The data are summarized in Table 1.

Sinus bradycardia

Sinus bradycardia has recently been reported as another ECG abnormality found in infants without CHB born to anti-SSA/Ro-positive mothers. Brucato and colleagues [4] reported that among 24 otherwise healthy children whose EKGs were obtained within the first 3 days of life, 4 had sinus bradycardia, with a mean heart rate of 84 beats/min (range 70 to 90). Spontaneous resolution was observed within 15 days [4]. The existence of sinus bradycardia has been reported in two infants with anti-SSA/Ro antibodies [22] and is supported by findings in an experimental animal model [23] and a recent study *in vitro* [24].

However, as with QTc lengthening, the pathological nature of neonatal sinus bradycardia should be established cautiously [8,13]. A study of cardiac rate in 134 healthy newborn infants during a 24-hour period showed that mean lowest heart rate was 85 beats/min, and sinus bradycardia was diagnosed in 109 healthy infants at their lowest heart rate [25]. Additionally, as stated previously [8], we did not find any significant difference in mean heart rate when we compared the ECGs of 58 anti-SSA/Ro-positive children with those of 85 anti-SSA/Ro-negative children of the same age [8].

Myocardial abnormalities and anti-SSA/Ro antibodies

Late-onset dilated cardiomyopathy

Late-onset dilated cardiomyopathy developing despite the early institution of cardiac pacing (during the first 2 weeks of life in 15 children) has been reported in 16 infants with

Table 1

Summary of the conflicting data on QTc interval in adults and in infants

Group	Reference	Characteristic	Anti-SSA/Ro-positive group	Control group	*P*
Infants	[2]	No. of patients	21	7	
		Age (days)	90	7	NA
		QTc (ms)	442 ± 35	403 ± 16	0.001
	[3]	No. of patients	38	7	
		Age (months)	65.4	1.8	NA
		QTc (ms)	379 ± 26	332 ± 20	<0.0001
	[8]	No. of patients	58	85	
		Age (days)	13 ± 14	15 ± 16	0.31
		QTc (ms)	397 ± 27	395 ± 25	0.57
Adults	[9]	No. of patients	31	26	
		Age (years)	41 ± 15	49 ± 13	NA
		QTc (ms)	445 ± 21	419 ± 17	0.000005
	[20]	No. of patients	49	62	
		Age (years)	46	44	NS
		QTc (ms)	411 ± 19	403 ± 24	0.06
	[21]	No. of patients	32	57	
		Age (years)	37 ± 11	38 ± 12	0.58
		QTc (ms)	409 ± 30	409 ± 28	0.78

NA, not available; NS, not significant. Data are presented as means ± SD when available.

complete CHB [5]. Congestive heart failure emerged progressively at a mean age of 11.6 months (range 2 weeks to 30 months) in 13 children. Deterioration occurred later in life (between 3.7 and 9.3 years) in three others. Of the 16 infants, 4 died from congestive heart failure, 7 required cardiac transplantation, 1 was awaiting it, and 4 exhibited recovery of the shortening fraction. None of the 16 myocardial biopsies showed an active inflammatory infiltrate, and immunofluorescence studies were unrevealing. The authors found an approximately 5 to 11% risk for delayed dilated cardiomyopathy in infants with CHB [5]. These children therefore require close monitoring, not only of ECG and of adequate functioning of a pacemaker, but also of ventricular function.

Endocardial fibroelastosis

The association of EFE with autoantibody-mediated CHB was first described by Hogg in 1957 [26]. Nield and colleagues [6] have recently reported EFE predominantly involving the left ventricle in 13 children with complete CHB. The date of diagnosis was prenatal in half of the cases, and postnatal in the other half. Severe ventricular dysfunction was present in all cases, leading to death ($n = 9$) or cardiac transplantation ($n = 2$). Immunohistochemical staining demonstrated significant deposition of IgG and also of IgM and the presence of T cells in three out of every four cases, suggesting that a fetal factor might be involved in the immune process leading to EFE. Additionally, the authors reported three cases of severe EFE in children without CHB born to mothers with anti-SSA/Ro antibodies. These cases have been detailed elsewhere [7]. In agreement with this, we recently recognized four cases that were consistent with less severe EFE in the absence of CHB (N Costedoat-Chalumeau, Z Amoura, E Villain, L Cohen, J-C Piette, unpublished data). The areas of increased echogenicity were seen predominantly in the endocardial surface of the atrial area. In the last case, it was the hyperechogenicity feature that prompted the cardiologists to ask for a search for anti-SSA/Ro and anti-SSB/La antibodies in the healthy mother. Both were positive. Because no CHB was noticed and because the hyperechogenicity was located only in the atria, no treatment was given. Interestingly, the child developed a cutaneous neonatal lupus syndrome at 1 month of age. Therefore, CHB and EFE might be two different, although frequently associated, autoantibody-mediated manifestations of neonatal lupus erythematosus syndrome [6].

Morphological heart abnormalities and anti-SSA/Ro antibodies

Cardiac malformations

Classically, autoantibody-mediated CHB is supposed to affect children without major anatomic cardiac abnormalities that would be considered causal for the development of CHB. However, miscellaneous cardiac structural lesions have been reported in 16 to 42% of children with CHB born to anti-SSA/Ro-positive mothers [10,11]. The occurrence of these lesions has never been studied in the absence of CHB. In our series of 165 pregnancies with CTD and anti-SSA/Ro antibodies [8], we observed two major cardiac abnormalities (associated in one case with pulmonary hypoplasia) leading to therapeutic abortions. One other child required neonatal surgery for transposition of the great arteries, and one sibling of a child with CHB had a ventricular septal defect. In total, the rate of anatomical heart abnormalities in our study was 4 of 141 pregnancies (2.8%). This frequency is significantly higher than in the general population (0.54% of all births including fetal deaths and induced abortion in the European registry, EUROCAT [27]; $P = 0.008$).

Prospective studies, including data from therapeutic abortions, are needed for the correct evaluation of the frequency of major anatomic heart abnormalities associated with anti-SSA/Ro, but physicians should already be aware of this potential risk.

Treatment of CHB

Curative treatment of CHB and prophylactic treatment to prevent the recurrence of CHB are two major issues. Treatment is based on fluorinated steroids (dexamethasone or betamethasone) that are able to cross the placenta in an active form and may stop the immune process involving the fetal heart. Indeed, several reports suggest that curative treatment with fluorinated steroids is effective for fetuses with second-degree block [1,28] or hydropic changes associated with CHB [28]. No durable recovery from complete CHB has yet been published. However, fluorinated steroids may significantly improve the survival of fetuses with complete CHB [29].

As discussed previously, the treatment of fetal incomplete CHB may change in the future, depending on the results of the PRIDE study. Indeed, one of the goals of this study was to assess the efficacy of maternal dexamethasone in reversing or preventing the progression of CHB newly detected *in utero* [30]. However, it is first necessary to establish the true prevalence of fetal first-degree CHB and to demonstrate that first-degree CHB is a marker for more advanced destruction of the conducting system, and then to show that it definitely requires treatment.

Because there is no convincing evidence for the use of steroids as preventive treatment for a pregnant woman with a history of CHB, the prophylactic behaviour facing a pregnant woman with previous CHB is still undetermined. Additionally, major concerns have been raised by paediatricians regarding the fetal safety of fluorinated steroids, especially because of the suspected neurological toxicity of dexamethasone [31,32]. These concerns are sustained by concordant animal studies, retrospective data and randomized trials [32]. We have also reported a high rate of adverse obstetric events in patients treated with dexamethasone to prevent CHB, including spontaneous abortion, stillbirth, severe intrauterine growth restriction and adrenal insufficiency/hypoplasia [32]. These adverse events of treatment with dexamethasone are similar to those occurring in untreated Cushing syndrome [33].

Useful guidelines for the treatment of CHB *in utero* have been proposed by Buyon and colleagues [34]. We have proposed similar guidelines for the French registry of pregnancy with anti-SSA/Ro antibodies [35] except that, in view of the study by Baud and colleagues [31] underlining the risks for fetal brain associated with dexamethasone, we prefer to use betamethasone for this purpose.

Conclusion

The spectrum of cardiac manifestations associated with anti-SSA/Ro antibodies is undoubtedly expanding. In addition to the classical complete and incomplete CHB, there is progressive recognition of transient CHB, severe late-onset cardiomyopathy and endocardial fibroelastosis. Other possible manifestations such as sinus bradycardia or QTc interval prolongation are currently a matter of debate. Cardiac malformations associated with anti-SSA/Ro antibodies are still questionable. Further studies are needed to optimize treatment, but guidelines are already available.

Competing interests

The author(s) declare that they have no competing interests.

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