REVIEW ARTICLE

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Arrhythmias Presenting in Neonatal Lupus

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Abstract

Perfusion of human foetal heart with anti-Ro/SSA antibodies induces transient heart block. Anti-Ro/SSA antibodies may cross-react with T- and L-type calcium channels, and anti-p200 antibodies may cause calcium to accumulate in rat heart cells. These actions may explain a direct electrophysiological effect of these antibodies. Congenital complete heart block is the more severe manifestation of so-called "Neonatal Lupus". In clinical practice, it is important to distinguish *in utero* complete versus incomplete atrioventricular (AV) block, as complete AV block to date is irreversible, while incomplete AV block has been shown to be potentially reversible after fluorinated steroid therapy. Another issue is the definition of congenital AV block, as cardiologists have considered congenital blocks detected months or years after birth. We propose as congenital blocks detected *in utero* or within the neonatal period (0–27 days after birth). The possible detection of first degree AV block *in utero*, with different techniques, might be a promising tool to assess the effects of these antibodies. Other arrhythmias have been described in NL or have been linked to anti-Ro/SSA antibodies: first degree AV block, *in utero* and after birth, second degree (i.e. incomplete block), sinus bradycardia and QT prolongation, both in infants and in adults, ventricular arrhythmias (in adults). Overall, these arrhythmias have not a clinical relevance, but are important for research purposes.

Arrhythmogenicity and electrophysiological effects of anti-Ro/SSA antibodies

Based on the facts that there is no convincing evidence that maternal antibodies can cross the sarcolemma of a normal cardiac myocyte, essentially two major categories of mechanisms for congenital complete heart block (CHB) can be identified. The first is abnormal surface expression of intracellular SSA/Ro and SSB/La antigens, eventually induced by apoptosis [1, 2], viral infection [3], UV light and IFNγ treatment [4]. The other mechanism is the cross-reactivity of maternal antibodies with targets other than SSA/Ro and SSB/La antigens. Maternal antibodies were reported to cross-react with laminin and with human cardiac myosin heavy chain at a critical stage during foetal cardiac development [5, 6], but the L-type calcium channels seem particularly important in this hypothesis [7–10].

After preliminary reports, [11, 12] Boutjdir in an outstanding paper [7] showed that IgG-enriched fractions and anti-52-kD SSA/Ro antibodies affinity-purified from the sera of mothers whose children have CHB reversibly induce complete atrioventricular (AV) block in the human foetal heart perfused by the Langendorff technique. At 33 min of perfusion, complete AV block was observed with the presence of only *P* waves and missing QRS complexes. Reperfusion of the heart with antibody-free Tyrode's solution for 48 min resulted in partial and slow recovery. Superfusion of hearts with IgG fractions from mothers with affected children also induced bradycardia and AV dissociation. In contrast, IgG from control mothers did not have any measurable effect on AV conduction. In the same paper, the authors showed that anti-Ro/SSA antibodies inhibit L-type Ca^{2+}currents at the whole-cell and single-channel level. Immunization of female BALB/c mice with recombinant 52-kD SSA/Ro protein generated high-titre antibodies that crossed the placenta during pregnancy and were associated with varying degrees of AV conduction abnormalities, including complete AV block, in the pups. These findings suggest that anti-52-kD SSA/Ro antibodies are causally related to the development of CHB.

The same group reported that the passive transfer of human anti-Ro/SSA into pregnant mice induced

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bradycardia and first degree AV blocks in the pups [8]. However, the penetrance was extremely low, paralleling human disease frequencies. Similarly, we reported the occurrence of sinus bradycardia in newborns of anti-Ro/SSA-positive women [13]. The rationale is that impulse generation at the sinoatrial node and conduction at the AV node critically depends on ICa-L.

In other experiments, the Swedish group [14] showed that maternal autoantibodies directed to a specific epitope within the leucine zipper amino acid sequence 200–239 (p200) of the Ro52 protein correlated with prolongation of foetal AV time and heart block.

QT interval prolongation has been inconsistently observed both in infants exposed to anti-Ro/SSA and in anti-Ro/SSA-positive adults [15, 16]; a clear physiological basis for this possible effect is lacking at present, even if it has been hypothesized [17].

Clinical features

Complete AV block (Congenital complete heart block; third degree AV block)

Third degree AV block is the most severe manifestation of neonatal lupus as it is irreversible and carries a high morbidity and mortality rate. The presence of signs or symptoms is mainly related to the ventricular rate, which usually ranges between 30 and 100 beats/min [18, 19], but may be also related to the cardiac contractility and to the ratio of atrial to ventricular contractions; heart rate usually declines during the pregnancy [20], the lower the rate, the higher the possibility of foetal hydrops and neonatal cardiac failure, and foetal or neonatal death correlates with a ventricular rate *in utero* ≤55 bpm [18–21].

Complete heart block (CHB) (either first, second, or third) is most frequently detected *in utero* by prenatal ultrasound, between 18 and 24 weeks of gestational age. This "window" coincides with the timing of placental transfer (that becomes effective at about 12 weeks) and the timing of the development of the human foetal conduction system which is formed by 12 weeks (thus explaining the absence of associated structural abnormalities) but presumably undergoes further remodelling. In the majority of cases, complete block requires a pacemaker implantation, frequently but not necessarily in the neonatal period. *In utero* death is usually related to intractable heart failure, but may be sudden and unexpected (personal observation).

Differential diagnosis: complete AV block (third degree) vs incomplete AV block (second degree). At first appearance of a foetal bradycardia, it can be difficult and time-consuming to differentiate between certain types of second degree (incomplete) AV blocks and third degree (complete) AV block, but this distinction might be important, as complete AV block to date is irreversible, while incomplete AV block has been shown to be potentially reversible after dexamathasone or bethametasone therapy [22, 23]. The distinction is critically dependent on the analysis of the relationship between atrial and ventricular contractions during foetal echocardiography. If the block is complete (third degree), atrial and ventricular contractions are completely dissociated. If the AV block is incomplete, second degree, some atrial contractions are not followed by ventricular contractions. Problems in particular may arise if the incomplete AV block has a fixed ratio 2:1 between atrial and ventricular contractions; in fact, this sequence may be difficult to ascertain echographically, with the consequence that an incomplete second degree AV block (potentially reversible) may be erroneously considered as complete (irreversible) [23]. Also blocked atrial premature contractions might be misinterpreted as second degree block.

Definitions, implications, and the problem of anti-Ro/SSA-negative blocks. Immunologists and rheumatologists understand as congenital a block "existing at or dating from birth". In contrast, cardiologists often use Yater's criteria: "heart block established in a young patient. There must be some evidence of the existence of the slow pulse at a fairly early age and absence of a history of any infection which might cause the condition after birth: notably diphtheria, rheumatic fever, chorea and congenital syphilis" [24]. Thus, it is evident that when immunologists, cardiologists, and obstetricians write about CHB, they may not be describing the same clinical or pathological entity [25].

To reduce the existing confusion in the literature, we recommended a change from the existing definition (Yater 1929).We proposed a new definition of isolated congenital complete AV block, acceptable to cardiologists, rheumatologists, immunologists, obstetricians, paediatricians: *"an AV block is defined as congenital if it is diagnosed in utero, at birth, or within the neonatal period (0–27 days after birth)"* [25, 26]. Accumulated data reveal that the large majority of cases detected *in utero* and not associated with structural heart defects causally linked with CHB are associated with the presence of anti-Ro/SSA antibodies in the mothers, while heart blocks detected after birth are generally not associated with maternal autoantibodies [25, 27]. The percentages of anti-Ro/SSA positivity vary according to the laboratory method employed (counterimmunoelectrophoresis, immunoblot, ELISA-commercial kits, ELISA-home made) as different methods have different sensitivities and different specificities. Immunological studies using the most sensitive and advanced methods approach 100% of positivity [25, 28]. In these studies, there may have been a selection bias; in fact mothers may have been selected based on a diagnosed or suspected connective tissue disease, as these cases were collected mainly from rheumatological centres. On the other hand, cardiological studies generally report

lower percentages of anti-Ro/SSA-positive cases (e.g. 65%), but details of methods employed to detect the antibodies often are lacking [18, 21, 27, 28].

Anyway advanced (second or third degree) AV blocks detected in utero or at birth and definitely anti-Ro/SSA negative exist; in an unselected series of 45 consecutive cases, we observed that 20% were anti-Ro/SSA negative, a finding that surprised us but was confirmed in several laboratories, including Ed Chan lab. These anti-Ro/SSA-negative blocks were less stable and complete than the anti-Ro/La-positive ones [28].

Assessment of first degree AV Block *in utero*

Several methods have been developed with the aim to detect *in utero* early foetal abnormalities, particularly 1st degree AV block that might herald CHB. The American group have evaluated the mechanical PR interval [29]. By using the gated-pulsed Doppler technique, time intervals 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 ventricular cardiac cycle may be measured. Ninety-five pregnant women with anti-Ro/SSA antibodies completed an evaluable course in 98 pregnancies. The protocol included foetal echocardiograms performed weekly from 16 to 26 weeks' gestation. PR intervals >150 ms were considered prolonged, consistent with 1st degree block. Ninety-two foetuses had normal PR intervals. Neonatal lupus developed in 10 cases; four were neonatal lupus rash only. Three foetuses had 3rd degree block; none had a preceding abnormal PR interval, although in two foetuses >1 week elapsed between echocardiographic evaluations. Tricuspid regurgitation preceded 3rd degree block in one foetus, and an atrial echodensity preceded block in a second. Two foetuses had PR intervals >150 ms. Both were detected at or before 22 weeks, and each reversed within 1 week with 4 mg dexamethasone. No 1st degree block developed after a normal ECG at birth. Heart block occurred in three of 16 pregnancies (19%) in mothers with a previous child with CHB and in three of 74 pregnancies (4%) in mothers without a previous child with CHB or rash ($P = 0.067$). The authors concluded that prolongation of the PR interval was uncommon and did not precede more advanced block and that advanced block and cardiomyopathy can occur within 1 week of a normal echocardiogram without initial 1st degree block. Echodensities and moderate/severe tricuspid regurgitation merit attention as early signs of injury [29].

The Swedish group reported on weekly echocardiograms performed on 24 women with anti-Ro/SSA 52-kd antibodies, between 18 and 24 weeks of gestation, with two Doppler echocardiographic methods designed to estimate the time delay between hemodynamic events caused by atrial and ventricular depolarizations [30]. Foetal AV time intervals were longer, and heart rates were slightly lower compared to foetuses not exposed to anti-Ro/SSA antibodies. Eight foetuses had signs of 1st degree block. It is of note that the cut-offs for 1st degree block were lower than those reported by Friedman [29]. One of these foetuses (whose PR interval was abnormal in the Swedish study but would not have been considered abnormal in the US study) had progression to complete block, and another showed recovery from 2nd degree block to 1st degree block, with betamethasone treatment. In the remaining six foetuses, spontaneous normalization occurred before or shortly after birth [30].

An Israelian group proposed the tissue velocity–based foetal kinetocardiogram (FKCG) to detect first degree atrioventricular block in foetuses at risk [31]. FKCG was performed in 70 foetuses of 56 anti-Ro/SSA-positive mothers. Foetuses were monitored with weekly FKCG from 13 to 24 weeks' gestation and compared to 109 normal foetuses. FKCG was obtained readily in all foetuses; six showed 1st degree block (AV conduction time >2 z scores above normal mean) at 21 to 34 gestational weeks. Immediate maternal treatment with dexamethasone resulted in normalization of AV conduction in all affected foetuses within 3 to 14 days. The ECG PR interval immediately after birth was normal in all affected newborns. No child developed complete CHB or cardiomyopathy in the subsequent 1- to 6-year (median 4-year) follow-up.

What is unknown from these three studies is the natural history of so-called 1st degree block. There are no data on spontaneous reversibility, and progression to advanced block has not been reproducibly documented to date. This is critical and investigators are encouraged to share echocardiographic tapes to validate the reliability of this candidate biomarker [32].

Spectrum and progression of conduction abnormalities in infants born to mothers with anti-Ro/La antibodies

To ascertain the spectrum of arrhythmias associated with maternal anti-Ro/La antibodies, records of all children enrolled in the Research Registry for Neonatal Lupus were reviewed [33]. Of 187 children with CHB whose mothers have anti-Ro/La antibodies, nine had a prolonged PR interval on ECG at birth, four of whom progressed to more advanced AV block. A child whose younger sibling had 3° block was diagnosed with 1° block at age 10 year at the time of surgery for a broken wrist. Two children diagnosed *in utero* with 2° block were treated with dexamethasone and reverted to normal sinus rhythm by birth, but ultimately progressed to 3° block. Four children had 2° block at birth: of these, two progressed to 3° block. These data have important research and clinical implications.

Perhaps many foetuses sustain mild inflammation, but resolution is variable, as suggested by the presence of

incomplete AV block in some cases and progression to complete block in others. Importantly, as subsequent progression of less-advanced degrees of block can occur, an ECG (to identify clinically silent first degree block) should be performed on all infants born to mothers with anti-Ro/La antibodies.

QT interval prolongation

QTc prolongation reflects cardiac repolarization prolongation and increased repolarization inhomogeneity associated with an increased risk of arrhythmias; it is also seen in the presence of cardiac failure (e.g. ischaemic heart disease). On the other hand, in clinical practice, a mild perinatal QT prolongation has a questionable clinical significance as it usually normalizes within few months after birth.

Years ago, we observed an infant - born to an anti-Ro/SSA-positive mother - who presented a marked QT prolongation in the absence of AV conduction abnormalities. As it has been shown in a study of more than 33,000 infants that the risk of sudden infant death is 41 times greater when QTc>440 msec [34], we have then analysed the ECG tracings for QT interval measurement of other anti-Ro/SSA-positive infants who did not have CHB, as well as those of a control group of anti-Ro/SSA-negative infants born to mothers with autoimmune diseases but negative for these autoantibodies. The study was performed in 21 anti-Ro/SSA-positive and seven anti-Ro/SSA-negative infants. A standard 12-lead ECG, recorded during the first 6 months of life (mostly at the third month), was analysed for each subject. QT and RR intervals were measured in lead two from five non-consecutive beats by a single investigator who was blinded to the infant's antibody status. Corrected QT (QTc) was automatically calculated according to the Bazett's formula. Positive and negative infants did not differ significantly for PR interval and QRS duration, whereas QTc interval was significantly greater in the group with anti-Ro/SSA antibodies (442 ± 35 versus 403 ± 16 msec, $P = 0.001$). When we analysed the individual values of QTc, we observed that 9/21 (43%) of the infants with anti-Ro/SSA had a QTc >440 msec, the upper normal limit (97.5th percentile) established in the previously mentioned large prospective study of more than 33,000 infants [34]. By contrast, all infants without anti-Ro/SSA antibodies had a QTc within the normal limits [15]. We then followed the children with prolonged QTc to evaluate the relationship between electrocardiographic abnormalities and the disappearance of autoantibodies from the babies' circulation. Interestingly, we observed a concomitant disappearance of electrocardiographic abnormalities and of acquired maternal autoantibodies during the first year of life [35].

In agreement with these findings, Gordon have described that the QTc is longer in children of anti-Ro/SSA-positive mothers, and even longer in those with siblings with CHB [36].

These data on QT prolongation were then largely disproved by more recent and larger studies that did not show any QT prolongation in infants from anti-Ro/SSA-positive women.

The French group studied 165 consecutive pregnancies in 106 anti-SSA-positive women with connective tissue diseases (CTDs) [37]. ECGs obtained on 58 children of this group were compared with those obtained on 85 infants born to mothers with CTDs who were negative for both anti-SSA and anti-SSB. For ECGs recorded during the first 2 months of life, the mean ± SD PR interval was 96 ± 16 msec in the anti-SSA-positive group and 96 ± 13 msec in the anti-SSA-negative group ($P = 0.84$), with mean QTc values of 397 ± 27 and 395 ± 25 msec ($P = 0.57$) and mean heart rates of 141 ± 23 and 137 ± 21 beats per min ($P = 0.20$), respectively. No difference in the PR interval, QTc interval, or heart rate was observed for ECGs obtained between 2 and 4 months of life. When ECGs obtained at 0–2 months were compared with those obtained at 2–4 months, a physiological prolongation of the QTc interval was observed in both study groups. No sudden infant death or symptomatic arrhythmia occurred during the first year of life. The authors concluded that the ECG findings in children of anti-SSA-positive and anti-SSA-negative mothers were not significantly different [37]. However, this study was mainly retrospective. Thus, larger and prospective studies are needed to assess the real prevalence of these ECG abnormalities in the population of infants born to mothers with autoimmune diseases.

Also, the American group did not find any prolongation of QT interval in a prospective study of 98 infants, but in this study, a control group was lacking [29]. Thus, overall, QT prolongation as a consequence of autoantibody injury remains unproven.

An intriguing finding has been raised by Lazzerini, who showed in a ECG-resting study that anti-Ro/SSA-positive patients frequently (58% of the cases) show a QTc interval prolongation (with mean values above the upper normality limit of 440 msec) [16]. Thus, he hypothesized that anti-Ro/SSA antibodies may exert a direct arrhythmogenic effect, thereby providing patients bearing such antibodies with a high risk of developing arrhythmias, as QTc interval prolongation is a definite risk factor for arrhythmic sudden death in the general population. Conversely, a later study of Costedoat-Chalumeau [38] evaluating 32 anti-Ro/SSA positive in comparison with 57 anti-Ro/SSA-negative CTD patients (almost exclusively patients with SLE) found no differences in QTc interval duration.

In another study by Gordon, in which the SLE preponderance was less extreme, the QTc interval was reported to be longer in the anti-Ro/SSA positive than in the anti-Ro/SSA-negative group, and this difference, although not significant, indeed approached significance ($P = 0.063$) [39].

Starting from this background, a 24-hour electrocardiographic monitoring study was performed by Lazzerini to investigate the possible relation between QTc interval prolongation and incidence of ventricular arrhythmias as a possible expression of immuno-mediated electric instability of the myocardium in anti-Ro/SSA-positive adult patients [40] The study population consisted of 46 patients with connective tissue disease; 26 anti-Ro/SSA-positive and 20 anti-Ro/SSA-negative (control group) patients. With respect to the control group, anti-Ro/SSA-positive patients commonly showed QTc interval prolongation (46% versus 5%), and this abnormality, when present, persisted for the 24 h (global mean 24-h QTc interval 440.5 ±23.4 versus 418.2 ±13.2 ms); they also had a higher incidence of complex ventricular arrhythmias (i.e., Lown classes 2–5, 50% versus 10%) also in the absence of detectable cardiac abnormalities. In these patients, there was a direct relation between global mean 24-hour QTc interval and ventricular arrhythmic load independently of age and disease duration. These authors concluded that anti-Ro/SSA-positive patients seemed to have a higher risk of developing ventricular arrhythmias. The risk appeared related mainly to abnormalities in ventricular electrophysiological characteristics emerging in the clinical setting as QTc interval prolongation [40, 41].

Sinus bradycardia

We described in a previous paragraph how anti-Ro/SSA antibodies may cross-react with the calcium channels so interfering with the functioning of sinoatrial node, and Mazel reported that passive transfer of human anti-Ro/SSA and anti-La/SSB autoantibodies into naive pregnant mice induced bradycardia [9]. We observed similar findings in humans [13, 42]. In four infants, a significant transient sinus bradycardia was observed (heart rate <3° centile for age). Prenatal ultrasound foetal heart rate was normal; no perinatal complication (in particular, no metabolic or thermal problems) was observed, and possible causes of bradycardia in newborns were excluded, e.g. electrolytes' abnormalities and drug interferences. In all cases, bradycardia disappeared within 10 days after birth, with no sequelae. Two mothers had systemic lupus erythematosus and two had an undifferentiated connective tissue disease. Our observations indicate that sinus bradycardia and sinus node dysfunction do not occur only in experimental animals passively transfused with anti-Ro/SSA antibodies but that they might be detectable also in rare cases in human newborns. In the Research Registry for Neonatal Lupus, data on atrial rates were sought among the 187 records reviewed. Atrial rates of 78 foetuses were recorded *in utero* by echocardiogram; the mean rate was 138 bpm ± 17 SD, range 68–160. Three foetuses (3.8%) had atrial rates less than 100 bpm. The rate of one increased from 68 to 158 on postnatal ECG. The rate of the second increased minimally from 95 to 104 on postnatal ECG. The third had a rate of 95 bpm *in utero* and a postnatal ECG was not provided. Atrial rates from postnatal ECGs were available for 40 neonates; the mean rate was 137 bpm ± 20 SD, range 75–200. The one slow rate of 75 bpm was obtained during sleep and increased to 140 bpm when awake. In an additional child, the records stated sinus bradycardia; however, no ECG was available and subsequent records were not sent to the Registry [33].

The French group did not observe any case of sinus bradycardia in their cohort of 58 children [37].

Sinus bradycardia, first degree AV block, QT prolongation: where we are now?

As described previously, the field is confused, with contradictory findings. Some of these discrepancies are explained by the time of recording of ECG. In fact, normal values of infants ECG are strongly dependent on the age of the infants. In particular, 1- year follow-up clearly demonstrated that QT interval prolongation was transient and disappeared within the sixth month of life in almost all cases [43]. The best studies that we have for the moment are probably the two following ones. In fact, two useful prospective studies have been recently published by Italian groups. In the first study [44], electrocardiograms prospectively obtained from 51 infants born of anti-Ro/SSA-positive mothers were compared with those obtained from 50 control infants born of mothers with anti-extractable nuclear antigen (ENA)–negative connective tissue disease. One anti-Ro/SSA exposed infant developed complete CHB. No infant showed sinus bradycardia. First degree AV block at birth was observed in five study group and no control group infants, $P = 0.023$. First degree AV blocks spontaneously reverted during the first year of life. Mean corrected QT value of infants born to anti-Ro/SSA-positive mothers was slightly prolonged but did not reach statistical significance, when compared with the control group (0.404 s versus 0.395 s; $P = 0.060$).

In the second study [43], 60 anti-Ro/SSA-positive and 36 anti-Ro/SSA-negative autoimmune mothers were prospectively followed; ECG and/or ECG-Holter were performed on the offspring at 1st, 3rd, 6th, and 12th month. One of sixty-one foetuses of anti-Ro/SSA-positive mothers developed third degree block, one developed 2nd degree AV block (30th week). Corrected QT

interval ≥440 msec was observed in 13% of cases and in 20% of controls at the first ECG. ECG-Holter showed QTc prolongation ≥440 msec in 59% infants of anti-Ro/SSA-positive mothers and in 60% of controls, and QTc ≥470 msec in four infants of anti-Ro/SSA-positive group and in two controls. One baby in the anti-Ro/SSA-positive and two in the anti-Ro/SSA-negative group required beta-blockers. Genetic causes of QTc prolongation were excluded. This prospective study showed that ECG abnormalities (1st degree block and QTc prolongation) are frequent in infants of mothers with autoimmune diseases particularly if ECG-Holter is performed, independently of maternal autoantibody profile. One-year follow-up clearly demonstrated that QT interval prolongation was transient and disappeared within the sixth month of life in almost all cases. [43]. Finally, as some studies have reported cardiotoxicity and conduction or repolarization abnormalities in patients treated with anti-malarial agents, drugs which have been shown to cross the placenta, these authors also assessed the presence of possible correlations between QT interval prolongation and maternal therapy with hydroxychloroquine during pregnancy. The prevalence of QT interval prolongation was not significantly different in the neonates born to mothers treated with anti-malarials during pregnancy and in those born to mothers who did not receive them [43].

Key points

Many electrocardiographic abnormalities may probably be rarely present in infants born to anti-Ro/SSA-positive women (and perhaps also in anti-Ro/SSA-positive adults), but these abnormalities are mild and not clinically relevant, even if their study may be very important for research as are probably related to some cross-reactions of anti-Ro/SSA antibodies with ion channels.

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