CASE SERIES

Case Series of Congenital Heart Block: Mothers With anti-Ro Autoantibodies and the Risks to Their Offspring

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ABSTRACT

Introduction: Cardiac manifestation of congenital heart block (CHB) in neonates following maternal anti-Ro and anti-La autoantibodies is a serious complication of neonatal lupus with a prevalence of 1: 22000 live birth and is associated with high morbidity and mortality. Disturbance of calcium homeostasis which leads to electrical conduction abnormality and eventually fibrosis of the heart tissue is the well-known pathogenesis of CHB. Most of the babies with CHB ended up with third-degree heart block and need a pacemaker as it is an irreversible injury. **Case series:** Here, we reported four case series of neonatal lupus with cardiac manifestation in mothers with positive anti-Ro or anti-La which have been detected during pregnancy within 24 to 32 weeks of gestation. All four cases of newborns ended up with third-degree heart block which required a permanent pacemaker by the latest age of two months old. **Conclusion:** A better understanding of the aetiology of the development of CHB and identifying the risk factors in mothers is crucial for the outcomes of CHB newborns. Early diagnosis through early screening, enhanced diagnostic tools for CHB, and timely treatment of the mother may aid clinicians in better management and improve the survival rate of infants with CHB.
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Keywords: Congenital heart block (CHB); Neonatal lupus (NL); Third-degree heart block; anti-Ro/anti-La

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INTRODUCTION

Neonatal lupus (NL) is an acquired autoimmune disorder following transplacental transfer of maternal autoantibodies to the foetus, leading to foetal and neonatal disease. Congenital heart block (CHB) is known to associate with the presence of anti-Ro/SSA and anti-La/SSB antibodies in the mother and is characterised by a block in signal conduction at the atrioventricular (AV) node. The presence of autoantibodies in the mother is the most common cause of CHB and is considered a rare disease in the newborn with an incidence of 1: 15000 to 22000 live births and is associated with high morbidity and mortality. CHB affects the neonates' group, where the block affected the conduction process ultimately causing poor heart contractility and rhythm. The incidental finding of a bradycardic episode is commonly detected in the foetus or newborn up to 28 days of life. CHB is commonly diagnosed during pregnancy between 18 to 24 weeks of gestation during the foetal echocardiogram.

Anti-Ro autoantibodies, also known as anti-Sjogren syndrome-related antigen A (anti-SSA), are directed against Ro52 and Ro60 where the antigens can be found in the nucleolus or nucleus and cytoplasm, respectively. The function of Ro52 is to regulate the inflammatory process in the human body. Hence, the presence of anti-Ro/SSA is associated with the injury of the cardiac tissues, ultimately causing CHB. The anti-La or anti-Sjogren syndrome-related antigen B (anti-SSB) which targets La/SSB antigen plays an important role in regulating messenger mRNA stability (1). Unlike anti-La, which is specifically found in Sjogren syndrome (SS) or systemic lupus erythematosus (SLE), anti-Ro can be present in many autoimmune diseases. Furthermore, patients with positive anti-Ro may have symptoms or be completely asymptomatic. A study from Oklahoma revealed that the time intervals taken from the detection of anti-Ro and anti-La in the serum to the time of diagnosis for SLE were about 3.6 years (2). Meanwhile, another study on SS found that it took about 4 years for an asymptomatic patient with positive anti-Ro to become symptomatic (3). In our case series, three out of four CHB cases had no maternal history of connective tissue disease (CTD). As most patients with positive anti-Ro are asymptomatic, it is likely necessary to test for anti-Ro before conception to prevent foetal complications and

provide the best possible surveillance.

Most infants born with CHB require a pacemaker implanted permanently within the first year of life. Considering the condition's significant morbidity and mortality, it necessitates a high index of suspicion for early diagnosis and prompt therapy when indicated, in which the presence of a structural cardiac defect significantly impacts the prognosis and treatment of an infant.

CASE SERIES

Case 1: A 32-year-old primigravida was first managed by another hospital, had had serial foetal echocardiograms performed for foetal bradycardia, before being transferred to our facility for post-delivery management of the infant. Her foetus was diagnosed with third-degree heart block with foetal heart rate (FHR) of 60 to 70 beats per minute (BPM) after a detailed scan at 24 weeks of gestation. An echocardiogram at 35 weeks demonstrated a total heart block with a ventricular heart rate of 60 to 70 bpm and an atrial heart rate of 100 to 110 bpm. Polyhydramnios and structural abnormalities such as a moderate atrial septal defect (ASD) and a large patent ductus arteriosus (PDA) were detected during the scan. The mother was asymptomatic and was investigated for SLE due to foetal bradycardia and a significant family history of SLE. Her mother and sister were both diagnosed with SLE. Serum for antinuclear antibodies (ANA) was detected with a speckled pattern and a titre of 1: >1280. Further immunological testing revealed that serum for extractable nuclear antigen (ENA) was positive for anti-Ro/SSA, anti-La/SSB, and anti-SmD autoantibodies. Her serum C3 and C4 levels were normal. The mother was initially started on hydroxychloroquine (HCQ) at 30 weeks of gestation and stopped one week post-delivery. A baby boy was born via planned lower segment cesarean section (LSCS) at 35 weeks with a birth weight of 2.77 kg, heart rate of 80 bpm, and an Apgar score of 6 and 8 at 1 and 5 minutes, respectively. His oxygen saturation ranged between 70 and 80%; consequently, he was intubated at 10 minutes of age for respiratory distress and was monitored in the Pediatric Cardiac Intensive Care Unit (PCICU). A few hours later, the heart rate dropped to 55 bpm, prompting the cardiology team to decide on an urgent permanent pacemaker (PPM). Postoperatively, the infant required a low dose of ionotropic support with a PPM rate of 120 bpm. During his admission to PCICU, he developed an episode of hospital-acquired infection (HAI) which he recovered well following courses of antibiotics. He was successfully extubated at the age of two months and discharged one week later with further follow-up.

Case 2: A bradycardic female neonate was delivered electively via LSCS at 35 weeks of gestation by a 27-year-old mother, who was gravida 3 para 1+1. The neonate was diagnosed with second-degree heart block during a routine foetal echocardiogram at 28 weeks of gestation with a ventricular rate of 75 to 120 bpm and an atrial rate of 120 to 140 bpm. Intravenous dexamethasone was completed by the mother at 32 weeks of gestation. The mother was asymptomatic, has no family history of autoimmune disease, and no previous history of CHB on her first pregnancy. In response to the echocardiography result of foetal bradycardia, tests for ANA and ENA were ordered. She had a positive ANA with a speckled pattern and a titre of 1:1280, and her ENA was positive for anti-Ro and equivocal for anti-La autoantibodies. Following LSCS, the infant was born with a heart rate between 70 and 80 bpm. The baby required non-invasive ventilation (NIV) immediately after delivery due to mild tachypnoea and was transferred to the PCICU for observation. The infant's heart rate remained above 75 bpm. An electrocardiogram (ECG) revealed a complete heart block with a ventricular rate of 63 to 91 bpm and a QT interval of 660 milliseconds (normal 400 to 440 ms). No structural abnormalities were observed by the echocardiography. The mother was informed of the infant's condition and the need for referral to a cardiac center (QTc syndrome). The infant was discharged on day 13 of life, with a follow-up at the National Heart Institute. PPM was successfully inserted when the girl was two months old following the exclusion of secondary causes of QT prolongation and confirmation by genetic testing.

Case 3: A 37-year-old lady, gravida 5 para 4, with underlying hyperthyroidism, who defaulted treatment had delivered a baby boy with complete heart block via an emergency LSCS at 38 weeks of gestation. Initial foetal bradycardia was identified on a foetal echocardiogram during regular follow-up at 35 weeks of gestation, with a ventricular rate of 65 to 67 bpm and an atrial rate of 128 to 130 bpm, suggesting a complete heart block. Two weeks of oral dexamethasone 4mg OD were given, and CTD screening was carried out following the echocardiogram findings. Her ANA test was reactive, with a speckled pattern and a titre of 1:1280, while her serum C3, C4, and thyroid function test (TFT) were normal. The patient was tested positive for anti-Ro/La autoantibodies. Her baby weighed 3 kg, and his Apgar scores at 1 and 5 minutes were both 8/8. The infant was subsequently admitted to the PCICU for continuous observation. The infant was intubated after 10 hours of life due to respiratory difficulties. His heart rate remained above 60 beats per minute without ionotropic support. An echocardiogram detected structural abnormalities such as patent foramen ovale (PFO) and mild tricuspid regurgitation (TR). A PPM was implanted on day 9 of life. The infant was discharged after two months, on day 51 of life, when an HAI had resolved.

Case 4: A 28-year-old, primigravida, was diagnosed with SLE for seven years. She was anti-Ro/La seropositive and had radioactive iodine therapy done ten years ago for multinodular goitre. She has been on L-thyroxine since then. Other blood tests, including TFT results, were normal. HCQ and dexamethasone were administered prior to pregnancy in anticipation of CHB. A foetus with a complete heart block was detected at 23 weeks of gestation. She had delivered a preterm baby boy at 33 weeks via LSCS for foetal cardiovascular compromise secondary to complete heart block with a birth weight of 1.97 kg. He presented with bradycardia with heart rate of less than 60 bpm and respiratory distress, for which he was intubated and monitored in the PCICU. Despite increasing doses of isoprenaline infusion, a β-adrenergic agonist, the infant's heart rate remained constant at 50 to 60 bpm. Bedside echocardiography revealed moderate ASD with large PDA. The cardiothoracic surgeon decided on temporary pacemaker insertion. The baby developed ventricular fibrillation upon pacing, requiring defibrillation intraoperatively and four ionotropic support post-pacemaker insertion. The pacemaker insertion was successful. However, the baby developed HAI and had difficulty weaning from ventilator support. On the 120th day of life, he was transferred to the closest hospital to his home, where he continued to require a high-flow nasal cannula (HFNC) 5 L/min. Nevertheless, the current infant's status was unknown as there was no further follow-up from this facility.

DISCUSSION

Neonatal lupus might develop with cardiac and non-cardiac symptoms; non-cardiac symptoms can manifest as disorders of the skin or liver or involvement of the haematological system. Most of the time, non-cardiac symptoms are transitory following elimination of maternal autoantibodies from the infant's circulation after several months. In contrast, cardiac neonatal lupus has the most detailed and complex presentation, whereby its effect is literally irreversible. CHB is the most severe form of neonatal lupus and is irreversible when it is associated with complete heart block with requires pacemaker insertion. It is associated with high morbidity and mortality with overall mortality of CHB is about 17.5% and 70% of children with CHB required permanent pacemaker (PPM) by the age of 10 years old (4). The prognosis is even worse when CHB is associated with a cardiac structural abnormality. In addition, according to a European study, approximately two-thirds of infants with autoimmune CHB needed pacemakers within 10 days of birth. In our four CHB cases, PPM was inserted in the infants as early as day one of life (5). The timing of PPM insertion in CHB is a complex decision that requires a comprehensive evaluation of each case based on various factors, including the severity of the heart block, the degree of symptoms, and the potential risks of delaying intervention. As in the second and third CHB cases, insertion of PPM on the tenth day of life is still deemed early intervention in neonates to allow for careful monitoring and evaluation of the patient's clinical status before the procedure.

Since anti-Ro crosses the placenta at 12 weeks of pregnancy, it is beneficial if anti-Ro/La is considered as a preconception testing or as soon as possible, preferably at the beginning of the first trimester, in those at high risk of anti-Ro, such as mothers with autoimmune disease or family history of CTD-positive for immediate treatment thereby preventing further development of heart block (6). Other than pre-existing autoimmune disease, patients with symptoms of CTD but negative for laboratory investigations towards the CTD, or those who have history of neonatal lupus or CHB in previous pregnancy should also be tested for the presence of these autoantibodies. For instance, there is a 50% chance of foetal CHB in subsequent pregnancies for women who have had two previously affected pregnancies (5). Hence, early detection of autoantibodies, proper monitoring of the foetal echocardiogram, and prompt treatment for high-risk mothers can slow the progression of the irreversible injury to the foetal heart. Despite the fact that mothers with elevated levels of anti-Ro and anti-La are frequently associated with severe foetal complications, there are only 14 known cases of CHB mediated by autoimmune in mothers with anti-La autoantibodies alone and this proves that anti-La alone should not be employed to predict autoimmune CHB (5). However, another study indicated that the presence of anti-La antibodies on top of anti-Ro enhanced the incidence of CHB (7). Three mothers in our case series were positive for both anti-Ro and anti-La, and two of their infants had PPM implanted as early as day one of birth. On the other hand, an infant whose mother had an equivocal anti-La had the PPM inserted two months later.

Surprisingly, only 1% to 2% of anti-Ro-positive pregnancies result in CHB development, despite a well-established correlation with maternal anti-Ro/La antibodies, suggesting that additional variables are crucial for the heart block's development (8). At approximately 12 weeks of gestation, these anti-Ro antibodies begin crossing the placenta and reaching embryonic tissues. According to a study, these autoantibodies bound to the corresponding antigens were discovered only in the heart of a child with CHB and not in the brain, kidney, or skin eluates (6). Cross-reactivity between maternal antibodies and foetal cardiac components regulating calcium-dependent processes in the heart may induce conduction and cell death disruptions. Eventually there will be reduced calcium release thus reduce contractility of the heart tissue. Another pathogenic mechanism that may involve in the development of CHB is incomplete removal of

Table I : Comparison of cases of infant with congenital heart block (CHB) to a mother with seropositive of anti-Ro/La autoantibodies

Case	Case 1	Case 2	Case 3	Case 4
Maternal age (years old)	32	27	37	28
Pregnancy	G1P0	G3P1+1	G5P4	G1P0
Maternal illness	nil	nil	hyperthyroidism	SLE, hypothyroidism (post RAI for MNG)
Symptoms	nil	nil	nil	nil
Family history	SLE (mother and sister)	nil	nil	nil
Time HB diagnosed	24 weeks	28 weeks	31 weeks	23 weeks
Maternal ANA IF	Positive	Positive	Positive	Positive
(pattern, titre)	speckled, > 1:1280	speckled, 1:1280	speckled, 1:1280	speckled, 1:1280
ENA	anti-Ro: positive anti-La: positive anti-SmD: positive	anti-Ro: positive anti-La: equivocal	anti-Ro: positive anti-La: positive	anti-Ro: positive anti-La: positive
Maternal treatment	HCQ (30 weeks POA)	nil	Steroid (35 weeks POA)	HCQ, Steroid (prior to pregnancy)
Offspring cardiac structural abnormality	Moderate ASD, large PDA	No	PFO, mild TR	Large PDA, Moderate ASD
Syndromic baby	No	No	No	No
Condition at birth	Intubated	NIV (CPAP)	Intubated	Intubated
Degree of HB	Complete HB	Complete HB	Complete HB	Complete HB
FHR at birth	55-70 bpm	60-70 bpm	60-70 bpm	50-60 bpm
PPM	Yes (Day 1 OL)	Yes (2 M.O)	Yes (Day 9 OL)	Yes (Day 1 OL)

G: gravida, P: para, SLE: systemic lupus erythematosus, ANA: antinuclear antibodies, IF: immunofluorescence, POA: period of amenorrhoea, ASD: atrial septal defect, PDA: patent ductus arteriosus, PFO: patent foramen ovale, TR: tricuspid regurgitation, NIV: non-invasive ventilation, CPAP: continuous positive airway pressure, HB: heart block, FHR: foetal heart rate, BPM: beat per minute, PPM: permanent pacemaker, OL: of life, M.O: month old, ENA: extractable nuclear antigen, RAI: radioactive iodine, MNG: multinodular goitre, HCQ: hydroxychloroquine

apoptotic debris via their opsonisation by maternal antibodies, and subsequent elimination by macrophages may result in persistent inflammation in the foetal heart, eventually causing irreversible damage to the developing heart. The low incidence of CHB in the offspring of mothers with anti-Ro/La antibodies is also attributable to genetic polymorphism. The tumor necrosis factor-alpha (TNFα) polymorphism was more prevalent in affected and unaffected children than in healthy controls. On the other hand, transforming growth factor-beta (TGFβ) polymorphism was significantly more prevalent in children with CHB than in their unaffected siblings (9). In addition to anti-Ro/La antibodies, antibodies against calreticulin, M1 muscarinic acetylcholine receptors, α-enolase, α-fodrin, and serotoninergic 5-hydroxytryptamine (5-HT4) receptors may contribute to CHB. Given the minimal likelihood of CHB development in anti-Ro-positive mothers, it is recommended to identify any potential risk factors. As in our fourth case, HCQ and dexamethasone were administered early before conception since she had a history of SLE. Despite early intervention, the infant developed a severe complete heart block, necessitating PPM on day one of life. However, research on these autoantibodies remains restricted, and the relevance of in vitro findings to the pathogenesis of heart block remains unknown (8).

Previous studies have shown that anti-Ro antibody titres greater than 50 UI/ml independent of anti-La antibody titres are associated with a 15% probability of having cardiac complications and a significant chance of getting a structural deformity and 5% of complete atrioventricular (AV) block in the foetus (10). Moreover, another study concluded that limiting serial foetal echocardiograms to women with elevated anti-Ro antibody levels above 50 UI/ml is safe. In addition to its cost-effectiveness, the titre is vital for guiding clinicians in the management of only a subset of patients. However, these autoantibodies were only detected qualitatively in all four of our cases. Therefore, a quantitative or at least a semi-quantitative result of the autoantibodies is essential for a more reliable

prognosis of foetal outcome and surveillance by echocardiography throughout pregnancy.

Recent evidence from a small observational study demonstrates that hydroxychloroquine (HCQ) which inhibits toll-like receptor signalling during the immunological response, may prevent CHB in foetuses at risk from anti-Ro-positive pregnant mothers or recurrent CHB in pregnant mothers with a previously affected baby (11). In these case series, HCQ is appropriate for pregnancies with a high CHB risk, such as the mother in Case 1, who had a significant family history of SLE, and the mother in Case 4, who had a prior diagnosis of SLE. Alternative options include fluorinated steroid treatments, which have been studied due to their anti-inflammatory properties, accessibility, easy administration, and affordability (12). It has been recommended that anti-Ro-positive mothers be referred for foetal echocardiogram surveillance beginning in the early second trimester due to the theory that the inflammatory consequences caused by antibody exposure may be prevented if identified and treated at an early stage (16–18 weeks) to improve the outcome of the foetus in the first and second-degree heart block (12). In contrast, A. Michael et al. has determined in their systematic review that fluorinated steroids offer no meaningful benefit to foetuses with CHB. Except for reversion to a lesser degree of heart block, it has little effect on foetal or neonatal survival (13). As in three of our case series, the initial echocardiography performed between 23 and 31 weeks of pregnancy revealed that there was already presence of irreversible heart block, and serum for anti-Ro autoantibodies was only obtained after the incidental finding of a foetal echocardiogram.

CONCLUSION

Maternal anti-Ro antibodies can have long-term consequences to their offspring. Early screening of asymptomatic mothers with seropositive anti-Ro antibodies as part of the antenatal workup may save the baby by preventing CHB progression through foetal echocardiogram surveillance and prompt treatment. Anti-Ro titres and the presence of additional autoantibodies like anti-La are predictive of the severity of CHB, and identifying other autoantibodies and genetic diversity could assist clinicians in managing CHB.

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