

Anti-Ro antibodies and complete heart block in adults with Sjögren's syndrome

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Abstract

There are emerging case reports worldwide of complete heart block in adults who test positive for anti-Ro antibodies and the underlying primary Sjögren's syndrome (pSS). The association between fetal/congenital cardiac abnormalities and transplacental transfer of anti-Ro antibodies is well established; there is, however, an ongoing debate about the underlying mechanism of activity of these antibodies in the cardiac tissue. In the past, maternal cardiac tissue was believed to be resistant to these pathogenic effects. This case highlights the need to change our understanding of how these antibodies cause adverse arrhythmogenic cardiac effects in adults. We present the case of a 44-year-old female with pSS and positive anti-Ro autoantibodies, who was diagnosed with autoimmune-induced complete heart block after presenting with dizziness and palpitations. She required insertion of a permanent cardiac pacemaker and has made a full recovery. Although the arrhythmogenic effects are rare, it may be that cardiac conduction in adults is not as resistant to anti-Ro antibodies as proposed.

Keywords: Arrhythmia, heart block, Sjögren's syndrome, autoantibody, autoimmunity, cardiac pacemaker

Introduction

Primary Sjögren's syndrome (pSS) is a chronic autoimmune connective tissue disorder characterized by sicca symptoms and circulating auto-antibodies (usually anti-SSA/Ro or anti-SSB/La) affecting 0.3%-0.5% of the Western population, and it is known to be prevalent in females (9:1) (1). pSS typically presents in the fifth or sixth decade, and in addition to profound dryness of the oral, ocular, and vaginal surfaces, other clinical features include swollen salivary glands, fatigue, and musculoskeletal pain. Additional manifestations of pSS present in the skin, lungs, kidneys, and nervous system, and there is an increased risk of developing lymphoma (>40-fold risk) (1).

Anti-Ro (SS-A) and anti-La (SS-B) autoantibodies were identified in 1969 (2). In addition to being strongly associated with pSS, anti-Ro antibodies are also associated with other connective tissue disorders to a lesser extent, including systemic lupus erythematosus (SLE). Autoantigens to the anti-Ro antibody are ribonucleoproteins identified as 52 and 60 kDa. The antigen to anti-La is 47 kDa, a transcription termination factor for RNA polymerase (2). Anti-Ro antibodies are the most prevalent amongst patients with pSS (two-thirds of patients), and 30%-60% of the patients are thought to have both (2). One idea is that initial tissue damage, for example from a virus, could be responsible for triggering cell apoptosis and hence subsequent exposure of Ro and La antigens (2). When Ro and La antigens present themselves at the surface of apoptotic cells, this causes Ro and La antibodies to be generated. Exocrine-gland epithelial cells are subsequently destroyed by auto-immune inflammatory activity through the up-regulation of tissue-damaging molecules and lymphocytic infiltration (2).

There is already a well-established association between transplacental transfer of anti-Ro antibodies from seropositive pregnant mothers and fetal and congenital cardiac abnormalities (3). This connection has led some clinicians to call for anti-Ro antibody screening to be included as a part of standard antenatal blood testing (3). The mechanism of action of anti-Ro antibodies on fetal hearts remains in debate. Among infants with complete heart block due to neonatal lupus, anti-Ro/SSA and/or anti-La/SSB antibodies bind to fetal cardiac tissue, leading to autoimmune injury of the AV node and its surrounding tissues (4). Apoptosis induces translocation of Ro/SSA and La/SSB to the surface of fetal cardiomyocytes, which then bind and induce the release of tumor necrosis factor by macrophages resulting in fibrosis (5). In addition to inducing tissue damage, anti-Ro/SSA and/or anti-La/SSB antibodies inhibit calcium channel activation at the cardiac L- and T-type calcium channels; L-type channels are crucial for action



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Figure 1. Rhythm strip of our patient an actual patient pre-PPM insertion showing complete heart block



Figure 2. Rhythm strip of our patient an actual patient post-PPM insertion showing a paced rhythm

potential propagation and conduction in the AV node (6). It has been accepted that adult cardiac tissue is resistant to the above mechanism due to the presence of mature sarcoplasmic reticulum, a higher reserve of L-type calcium channels, and a lower susceptibility to apoptosis compared to fetal heart cardiocytes (7). We present a case of otherwise unexplained complete heart block occurring in an adult patient with underlying pSS and positive anti-Ro antibodies that poses a question regarding whether the adult cardiac conduction system is really resistant to the arrhythmogenic effects of anti-Ro antibodies.

Case Presentation

A 44-year-old-female, originally from the Philippines, was diagnosed with complete heart block after presenting with symptoms of dizziness and palpitations and had a background of pSS. She was originally diagnosed with anti-Ro-positive pSS in 2008 after presenting with joint pain and sicca symptoms. She also had a medical history of hypothyroidism, asthma, and pernicious anemia. She was being treated regularly with levothyroxine and hydroxocobalamin injections. She also used artificial saliva and tears for sicca symptoms but was on no other medical therapy to treat her Sjögren's syndrome. She had previous intolerance to hydroxychloroquine, which manifested as headaches. She had a family history of diabetes, stroke, and ischemic heart disease, but no family history of sudden cardiac death or cardiac conduction problems. When she presented 8 years after the pSS diagnosis with symptoms of dizziness and palpitations, on examination, the patient was found to have a pulse rate of 42-46 beats/minute, blood pressure 105-120/60-62 mmHg, and oxygen saturation of 97%. The cardiovascular examination was otherwise normal with no additional heart sounds and with a normal jugular venous pressure. The respiratory examination was also normal

as well. Intermittent complete heart block was detected on cardiac monitoring (Figure 1). The cardiac magnetic resonance imaging showed a normal cardiac/major vessel anatomy. Ventricular function was preserved, although biventricular dilatation was present, but there was no evidence of ischemic pathology, and left ventricular ejection fraction was 70%. The patient had a hemoglobin level of 12.3 g/dL and troponin T < 14 ng/L. Anti-Ro-60 antibodies and anti-La antibodies remained positive. The thyroid function was well controlled with TSH levels consistently ranging from 1.8 mU/L to 3.57 mU/L. Due to no other explainable mechanism, a diagnosis of autoimmune mediated complete heart block was made. A dual-chamber permanent pacemaker (PPM) was inserted without immediate complications (Figure 2), although the patient later developed lower respiratory tract infection that required a prolonged hospital stay. At the cardiology follow-up and pacemaker check, there was a normal pacing and sensing function.

Written informed consent was obtained from the patient.

Discussion

There are several reported cases worldwide of adult conduction abnormalities in the presence of circulating anti-Ro antibodies. A 76-year-old female was diagnosed with underlying Sjögren's syndrome and hypopituitarism after presenting with syncope, requiring an emergency pacemaker for life-threatening first-degree heart block (8). There is another report of a 49-year-old anti-Ro-positive female who presented with dizziness and was diagnosed with Sjögren's syndrome. She was found to have variable degrees of heart block on Holter monitoring (2:1, 3:1, Complete). A PPM was inserted, and intra-cardiac electrocardiogram (ECG) revealed an infra-His block (9). Lazzarini conducted a systematic review that

identified cases of unexplained complete heart block with a background of connective tissue disease. This revealed more than 70% of patients to be positive for anti-Ro antibody (16/21) (7). Three percent of the population have anti-Ro antibodies without systemic disease; however, there is other evidence that identifies anti-Ro-antibody-positive patients with Sjögren's syndrome who developed complete heart block in the absence of structural heart disease (7). Santos-Pardo et al. described a case in 2013 of a 26-year-old female presenting with complete heart block due to circulating anti-Ro antibodies whose condition was reversed after initial intravenous methylprednisolone therapy followed by maintenance immunosuppressive therapy with low-dose methylprednisolone and azathioprine (10).

Although resultant arrhythmogenic effects are rare, it may be that cardiac conduction in adults is not as resistant to circulating anti-Ro antibodies as previously thought. Further research is warranted to understand the pathogenicity of these antibodies, their action on adult cardiac tissue, and as referred to above, potential for reversibility. With an increasing number of case reports, testing for anti-Ro antibodies should be considered in patients with complete heart block, where structural, biochemical, and electrophysiological causes have been excluded, even in the absence of an established connective tissue disorder.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

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