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Sinus node dysfunction as an initial presentation of adult systemic lupus erythematosus

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Running title: Sinus node dysfunction and SLE

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Case report

A 27-year-old previously healthy female presented with a 4 day history of intermittent fever and photosensativity, facial rash, morning stiffiness, oral ulcers, generalized myalgia, arthragia, and hair loss. An antinuclear-antibody (ANA) titer was 1:80 with a cytoplasm pattern and 1:40 with a nucleolar pattern. Her rheumatoid factor (RF) level was 25.5 IU/ml, serum anti-native DNA antibodies level was 620.2 U/ml, and serum immunoglobulin G level was 2100 mg/dl. The level of complement protein C3 was 37.1 mg/dl, and the C4 level was 2.01 mg/dl. Tests for antibodies to nuclear antigens (Sjogren's syndrome A/Ro, Sjogren's syndrome B/La, Smith), Beta2-glycoprotein, cardiolipin, and ribosomal P were negative, but for ribonucleaprotein (RNP) were positive. Base on the clinical presentation and laboratory data, she was diagnosed with

SLE. On the 5th hospital day, physical examination revealed a pulse of 41 beats/min and electrocardiogram (ECG) revealed sinus bradycardia (Figure). Echocardiopraphy revealed normal valvular structure and systolic and diastolic function. Myocardial infarction, ischemic heart disease, infections, hypothermia, hypothyroidism, raised intracranial pressure, high vagal tone, electrolyte imbalance and drugs related bradycardia were excluded by clinical evidences and laboratory data. Her abnormal ECG completely resolved 5 days after high-dose intravenous methylprednisolone infusion, and she was maintained successfully with a low dose of oral steroids.

Discussion

SLE, a connective tissue disease characterized by the production of the auto-antibodies and immune complexes, can affect all organs including the heart. Cardiac involvement in SLE has been reported, including pericarditis, myocarditis, valvular abnormalities, coronary heart disease, and conduction system disturbances[1]. Cardiac complications may develope either as incidental findings or in association with a lupus flare. Since the symptoms may be subtle, the occurrence and severity of the heart diseases are usually underestimated.

Conduction system disturbances in SLE are less commonly described[3]. Conduction disturbances with high grade AV block can be observed in neonatal period of infants born from mothers with SLE. The mechanism of neonatal heart block is considered to be due to

transplacental passage of maternal antibodies with injury of the conduction system by a direct cytotoxic effect of anti-Ro or anti-La antibodies[4,5]. However, high grade AV block is a rare complication of adults with SLE that may occur in the setting of an acute flare-up of the disease, as a sign of antimalarial toxicity, or as an initial manifestation[2,6,7-9]. Vasculitis selectively affecting cardiac conduction tissue without induction of overt myocarditis and vacuolar myopathy have been implied in its pathogenesis[10]. Anti-Ro, anti-La, and anti-RNP antibodies have also been proposed as markers of cardiac involvement in adults with SLE[11,12]. Pacemaker implantation is sometimes required in patients with irreversible conduction disturbance in spite of maximal steroid use or antimalarial withdrawal.

Sinus bradycardia may be a sign of sinus node dysfunction, ischemic heart disease, infiltrative disorders, infections, inflammatory disease, hypothermia, hypothyroidism, raised intracranial pressure, high vagal tone, electrolyte imbalance, and can be caused by certain drugs.[13] In the present report, the young female had no history of chest pain and no evidence of myocardial ischemia or infarction on ECG and echocardiography. Tests of thyroid function and serum electrolytes were within normal limits. There was also no clinical manifestations of increased intracranial pressure, hypothermia, or infection. No history of the use of drugs that can result in sinus bradycardia was noted. The patient's heart rhythm was continuously monitored by ECG monitor, and the profound sinus bradycardia was presented not only in the night, but also during the daytime, and therefore an association with the physiologic variation of heart rate was

excluded. In addition, no evidence of other cardiac conduction disorders such as atrioventricular block or bundle branch block were found by ECG monitoring. Her abnormal ECG completely resolved 5 days after high-dose intravenous methylprednisolone infusion, and no recurrence of bradycardia occurred. Based on the above findings, short-term isolated sinus node dysfunction presenting as profound sinus bradycardia due to SLE is highly suspected.

In the present case, we addressed the issue of bradycardia in a young female. Further evaluation of the bradycardia is necessary because of the possibility of a serious underlying disorder and unfavorable outcome if not treated. A detailed history, ECG follow-up, and echocardiogrphy are essential for the differential diganosis of bradycardia. Laboratory tests for hypothyroidism, infection, inflammatory disease and connective tissue diseases should be performed. The tilting table test is recommended if the bradycardia occurs paroxysmally, and is suspected to be due to vagal tone variation or orthostatic change.[14] In addition, the occurrence of episodes of bradycardia are sometimes infrequent, and therefore may not be recorded during a routine ECG examination. Recordings over a longer period of time are frequently required for detection and assessment of the bradycardia. Holter ECG monitoring is recommended for the evaluation of suspected bradycardia, or further investigation of documented bradycardia in young females.[15] This can allow the severity and characteristics of the bradycardia to be further clarified. Based on 24-hour recording data, the possibility of bradycardia due to physiologic variation of cardiac rhythm can be excluded. Telemetry ECG monitoring is an alternative choice

for the evaluation of bradycardia in young patients.[15] It can provide a longer recording period than Holter ECG monitoring; however, the patient must stay in a telemetry unit. A loop recorder is also an alternative choice for non-invasive monitoring of bradycardia, and can provide a much longer period of recording.[15] Cardiac electrophysiological study is an invasive tool for the evaluation of the sinus node and cardiac conduction system. It can assist the investigation of the mechanism of bradycardia, and assess the results of therapy. Cardiac electrophysiological studies are recommended when the bradycardias occur paroxysmally and cannot be evaluated by non-invasive monitoring methods, or when a serious underlying mechanism is suspected.[16]

In the present case, echocardiography showed normal LV global systolic performance, which excluded overt myocarditis. Focal myocarditis or vasculitis due to a direct cytotoxic effect of auto-antibodies selectively affecting the sinus node without induction of diffuse myocarditis is the suspected underlying mechanism in the present case. Magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), and positron emission tomography (PET) have been recently described as useful for diagnosis of myocarditis. MRI has been reported to be a valuable tool for the evaluation and monitoring of inflammatory heart disease. Histopathological studies have indicated that the region of contrast enhancement in MRI is associated with active inflammation.[17] With PET, a pattern of 18F-fluorodeoxyglucose (FDG) uptake limited to cardiac structures is considered a sign of a local inflammatory process.[18] The role of SPECT myocardial perfusion imaging in patients with myocarditis is still unclear. Focal

areas of reversible hypoperfusion on SPECT imaging has revealed concordant findings with MRI in myocarditis.[19]

To the best of our knoweledge, sinus node involvement with sinus node dysfunction has not been reported as an initial presentation of SLE in adult patients. In our reported case, we excluded the major causes of sinus bradycardia, except for SLE. The patient's abnormal ECG completely resolved after high-dose intravenous methylprednisolone infusion. Sinus node involvement with significant bradycardia is one of the possible complications in the early stage of adult SLE.

In summary, sinus node dysfunction with profound bradycardia is a possible complication of early-stage adult SLE. We belive that the underlying mechanism is similar to AV node involvement in adult SLE, including infiltration of fibrotic granulation tissue secondary to inflammation, and small vessel vasculitis. A thorough cardiovascular history and periodic electrocardiographic monitoring are suggested for early detection of this complication in the acute phase of adult SLE.

Reference

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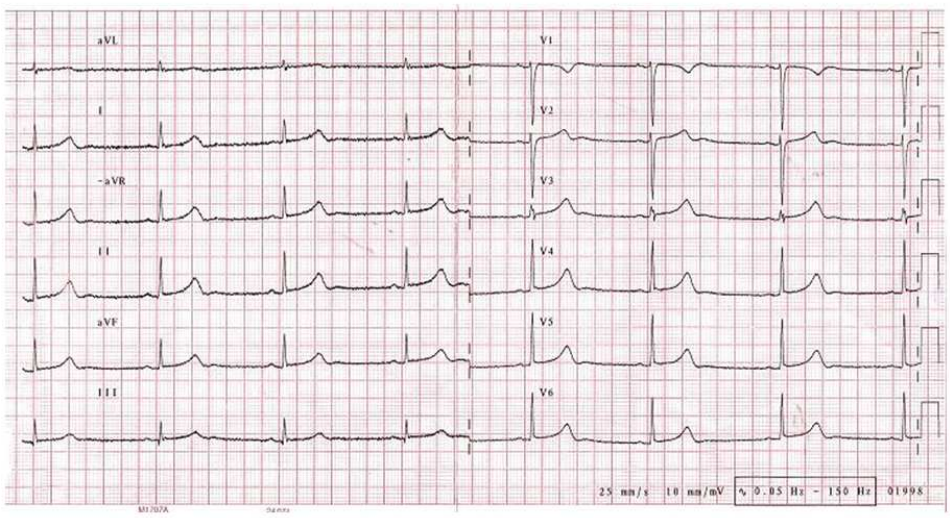
Figure Legends

Figure. ECG in the early stage of SLE reveals profound sinus bradycardia (ventricular rate = 41/min).



ECG in the early stage of SLE reveals profound sinus bradycardia (ventricular rate = 41/min).
254x190mm (96 x 96 DPI)

Responses to the Reviewer's Comments

Comments to the Author

Authors describe a young woman with initial features of systemic lupus, in whom incidentally, bradycardia is recognized. They suggest an association between systemic lupus and bradycardia, and hypothesized a dysfunction of the sinus node and possible myocarditis. In addition, they support the association between cardiac conduction system involvement and SLE because of the apparent resolution of bradycardia after the use of high steroid dose.

Response: Thank you for the detailed comments about this manuscript. They have proven to be very helpful.

Responses for specific comments:

1. Bradycardia might be a symptom of sinus node dysfunction, as well as other conditions, such as infiltrative disorders, infections, and inflammatory disease. Some diseases were ruled-out in this case. How can we rest assure that bradycardia was due to sinus node dysfunction and no other heart conduction system anomaly?

Response: Thanks for your comments. Sinus bradycardia may be a symptom of sinus node dysfunction, ischemic heart disease, infiltrative disorders, infections, inflammatory disease, hypothermia, hypothyroidism, raised intracranial pressure, electrolyte imbalance and can be caused by certain drugs. Based on the clinical evidences and laboratory data, we have

excluded the possibility of the above disorders except sinus node dysfunction. We have further discussed the above issue in the paragraph of discussion. (page 4; line 3-6 and page 5; line 10-19).

In addition, no evidence of other cardiac conduction disorders such as atrioventricular block or bundle branch block were found by ECG monitoring. Her abnormal ECG completely resolved 5 days after high-dose intravenous methylprednisolone infusion, and no recurrence of bradycardia occurred. Based on the above findings, short-term isolated sinus node dysfunction presenting as profound sinus bradycardia due to SLE is highly suspected (page 6; line 1-5).

2. It should be discussed what is the recommended steps in the study of a young woman with asymptomatic bradycardia, in order to point-out how other differd.ential diagnosis can be excluded. For instance, have patient's physicians performed a 24-h electrocardiogram registry to discard physiologic variation of cardiac rhythm? What could be the indication of electrophysiological mapping in this case?

Response: Thank you for your comments. We have discussed the above issues in the paragraph of discussion. The recommended steps and potential tools for differential diagnosis and further evaluation of the bradycardia in a young female have been listed in the discussion. We also provided some new references (page 6; line 6-19 and page 7; line 1-8).

3. Echocardiogram image is reported as normal, which excludes the presence of myocarditis. So, this image is maybe not useful for the case description. Other tools newly described for diagnosis of myocarditis in SLE patients should be talked about.

Response: Thank you for the comments. We have deleted the echocardiogram image in the manuscript. We have also described the tools newly described, including MRI, SPECT and PET, for diagnosis of myocarditis in SLE patients (page 7; line 9-19 and page 8; line 1-2).

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