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Systemic lupus erythematosus, syncope, high degree atrio-ventricular block and Hisian pacemaker

Lupus eritematoso sistémico, síncope, bloqueo auriculoventricular de alto grado y marcapasos de estimulación hisiana

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Palabras clave: *lupus eritematoso sistémico, bloqueo auriculoventricular, estimulación hisiana, bloqueo de rama derecha, síncope.*

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ABSTRACT

Introduction: Systemic Lupus Erythematosus (SLE) is frequently associated with ischemic heart disease, whereas other connective tissue diseases induce electrical conduction disturbances. **Presentation of case:** a 54-year-old female had SLE diagnosed in 2008 and systemic arterial hypertension. The patient presented with syncope and dizziness. The electrocardiogram (ECG) showed bradycardia, Right Bundle Branch Block (RBBB), and 2º Mobitz II Atrio-Ventricular Block (AVB) while having hypokalemia. The electrolyte unbalance was corrected. A Holter and new ECG showed RBBB, anterior fascicle block, and 2º Mobitz II AVB again. A stress echocardiogram was negative for ischemia and showed an antegrade Wenckebach phenomenon at 110 beats per minute (545 ms). That sort of AVB suggested high requirements of ventricular stimulation. Thus, a double chamber pacemaker (DDD) with Hisian stimulation was implanted without acute complications. The patient has been followed up for four years and showed important shifts in stimulation thresholds, impedance, and in the selective (or not) His capture, sometimes determined by atrio-ventricular delay. This prompted recurrent programming changes. **Conclusion:** His's stimulation in this subject has prevented new syncope episodes, but the behavior of stimulation thresholds and impedance in the presence of SLE seems unstable and requires frequent surveillance. Ventricular stimulation through the left bundle branch would now be preferred, but due to the scarcity of conduction disorders in SLE patients, more information is required.

RESUMEN

Introducción: *el lupus eritematoso sistémico (LES) suele asociarse con enfermedad isquémica cardiaca, a diferencia de otras colagenopatías que provocan trastornos de la conducción eléctrica.* ***Presentación del caso:*** *una mujer de 54 años con LES diagnosticado en 2008 e hipertensión arterial sistémica presenta síncope y mareos. El electrocardiograma (ECG) muestra bradicardia, bloqueo de la rama derecha (BRD) y bloqueo auriculoventricular (BAV) de 2o Mobitz II con hipocalemia. Se corrigió el trastorno electrolítico y se hizo Holter que muestra BAV 2o MII. Bloqueo de rama derecha del haz de His (BRD) y bloqueo de fascículo anterior del haz de His (BFAS). El ecocardiograma de estrés es negativo para isquemia, pero muestra un punto de Wenckebach anterógrado a 110 latidos por minuto (545 ms). El tipo de bloqueo presupone requerimientos de estimulación ventricular elevados y se implanta marcapasos de doble cámara (DDD) con estimulación hisiana sin complicaciones. Durante cuatro años de seguimiento ha habido variaciones importantes en los umbrales de estimulación e impedancia, así como en la captura selectiva o no selectiva del His, a veces asociada con el retraso auriculoventricular, por lo que es necesario hacer ajustes recurrentes en la programación.* ***Conclusión:*** *la estimulación hisiana ha prevenido nuevos síncopes en este caso, pero el comportamiento de los umbrales de estimulación e impedancia en presencia de LES es inestable y requiere de vigilancia frecuente. Se comenta la posibilidad de preferir estimulación de rama izquierda, pero dada la rareza de los trastornos de conducción en LES, se requiere de más información.*

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Abbreviations:
AVB = Atrio-Ventricular Block.
bpm = beats per minute.
BUN = Blood Ureic Nitrogen.
DDD = double chamber pacemaker.
ECG = Electrocardiogram.
LVEF = Left Ventricular Ejection Fraction.
PM = Pacemaker.
RBBB = Right Bundle Branch Block.
RNP = Ribonucleoprotein.
RNP = Systemic Lupus Erythematosus.
SLE = Systemic Lupus Eritematosous.

INTRODUCTION

Rheumatologic diseases are associated with cardiovascular disorders that may range from serositis to vasculitis-induced coronary artery disease and ischemia, valvular heart disease (Libman Sacks' endocarditis, for example) and even rhythm disturbances such as sinus node disease or Atrio-Ventricular Block (AVB) due to chronic inflammation and fibrosis. Systemic Lupus Erythematosus (SLE) is often associated with vasculitis and, thus, atherosclerotic ischemic heart disease.[1,2] Approximately 50% of SLE patients will show some cardiovascular disease.[3] The most common seems to be serositis (pericarditis is present in 25% of patients). Autopsy reports have shown myocarditis in up to 40% of SLE patients, but it is clinically evident in only 10% of them. This condition tends to disappear spontaneously, but it can progress to dilated cardiomyopathy, a substrate for tachycardia or bradyarrhythmia. It is noteworthy that 40% of SLE patients might have subclinical ischemic heart disease, but it will be manifested only in 12%. Unless there are advanced stages of myocardial disease derived from ischemia or myocarditis, the chances that SLE induces conduction disturbances are scarce, especially when there is no apparent inflammatory activity. This case shows a symptomatic advanced AV block in an SLE patient, without further evidence of cardiac or pericardiac involvement, that needed pacing with high requirements of ventricular stimulation.

CASE PRESENTATION

With previous consent from the patient, we present the case of a 54-year-old female who was evaluated by rheumatology in 2008 and diagnosed with SLE based on clinical criteria and antinuclear antibodies. The patient received prednisone and leflunomide as immunomodulators. She complained of frequent fatigue and occasional back and joint pain. Arterial hypertension was diagnosed in 2010 and received treatment with amlodipine and chlortalidone by internal medicine.

The patient was referred to a cardiology consultation in December 2019 because of syncope while washing her car and frequent dizzy spells. In that first evaluation, her electrocardiogram (ECG) showed a Right Bundle Branch Block (RBBB) with superior axis deviation, suggesting a concomitant anterior fascicle block, 2º Mobitz II AVB, and bradycardia. At that moment, she had a serum potassium level of 2.7 mEq/L with indicators of renal impairment (creatinine 1.3 mg/dL, urea 80 mg/dL, and Blood Ureic Nitrogen [BUN] 37.4 mg/dL) but normal general urine test.

The patient was started on volume and potassium repositioning. An echocardiogram showed a structurally normal heart with 57% Left Ventricular Ejection Fraction (LVEF) without segmental mobility abnormalities. When she reached a serum potassium level of 3.8 mEq/L, the ECG still showed the bifascicular block (RBBB and fascicle block), but the AVB was apparently corrected.

After discharge, a 24-hour Holter monitoring showed again 2º Mobitz II AVB during sleep periods, without significant pauses. Then, a negative-for-ischemia dobutamine-stress echocardiogram induced antegrade Wenckebach phenomenon at 110 beats per minute (bpm) (545 ms cycle length).

With this information and the evidence that the AV-block was symptomatic, a double chamber (DDD) pacemaker (PM) was proposed. Since the possibilities of high ventricular stimulation requirements were elevated, a bifascicular block was present, and the patient was 54 years old, a physiological stimulation approach was preferred, and thus, a His bundle stimulation device was implanted (Medtronic Ensura ENS01DR, Medtronic inc. Minneapolis, USA).

The procedure was performed without complications. The His-bundle stimulation

threshold was 1 V with a pulse width of 0.6 in unipolar stimulation. The impedance was 232 Ohms, and the R wave amplitude was 3.3 mV. The baseline QRS measured 160 ms, and after His stimulation, it shortened to 100 ms. *Figure 1* shows the baseline ECG as well as the ECG and chest X-ray control prior to discharge the day after PM implantation. The stimulated AV delay was set to 180 ms and the sensed one to 160 ms. Since then, the patient has not presented any new syncope events.

Four months after the implant, she reported dyspnea while housekeeping but not on exertion (brisk walking her dog). At that moment, the His stimulation threshold was 1.25 V and 0.4 ms with monopolar stimulation. The impedance had increased to 475 Ohms with no evidence of rupture or displacement of the electrode. With lower output voltage, there was non-His selective capture up to 0.5 V.

At the ninth follow-up month, she complained of a «twitching sensation» near the generator in the pectoral muscle. The ECG showed a loss of selective capture and right bundle branch block, apparently related to the monopolar stimulation. The PM was set to bipolar stimulation, and the sensation disappeared. The new selective capture threshold was 1.5 V with 0.5 ms pulse width.

During 2021, the patient did not receive presential follow-up visits because of the COVID pandemic, although she reported herself sometimes fatigued, with tolerable short bouts of joint pain and asymptomatic periods by e-mail communications.

In December 2021, during an office visit, the His stimulation threshold was again elevated (3.75 mV), monopolar stimulation was painful, and induced pectoral muscle contractions. His' output was again set to bipolar. At that point, the patient still showed RBBB morphology in stimulated beats. *Figure 2* shows the threshold, impedance, and sensitivity values during follow up.

In July 2022, she underwent a surgical left shoulder ligament repair, and in September, she had a *Clostridium difficile* gastric infection without any evidence of endocarditis.

Finally, in November 2023, the patient reported herself to be asymptomatic, active,

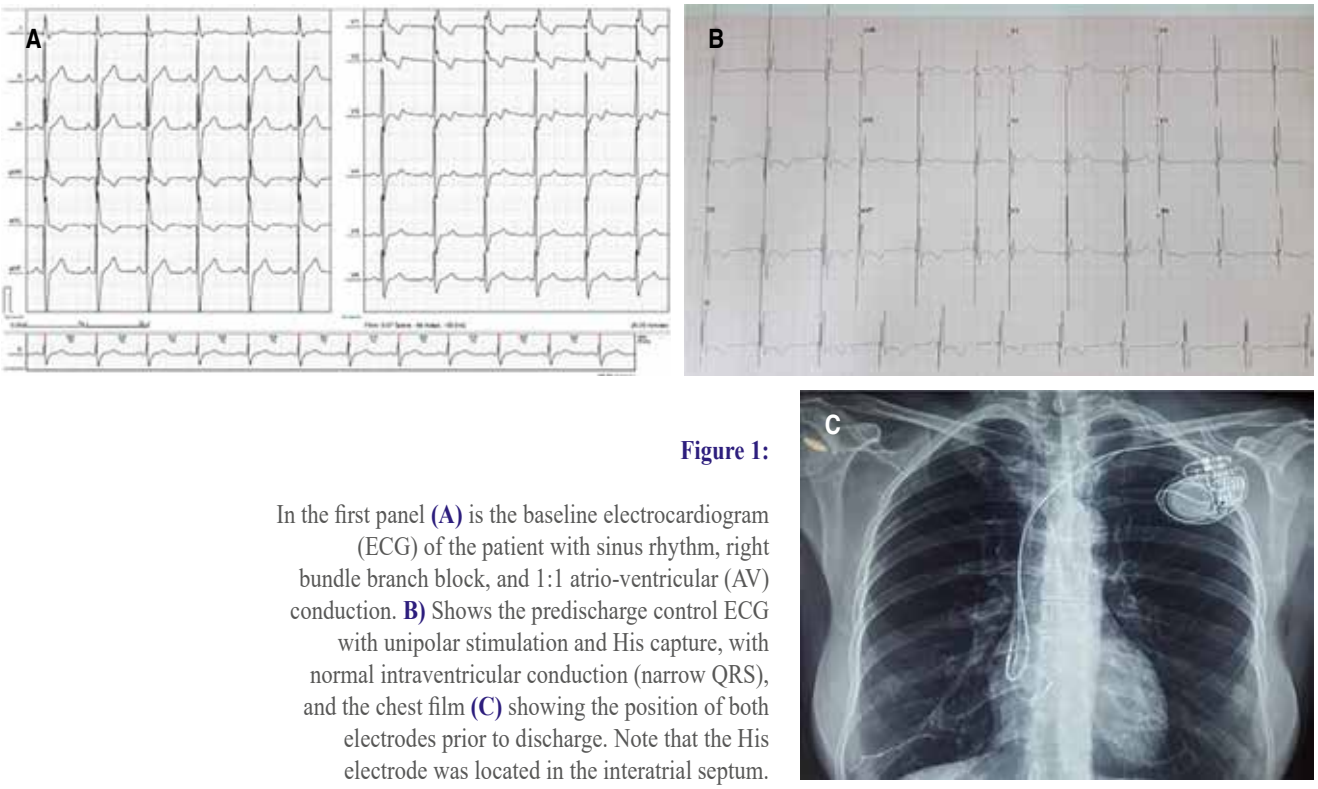

Figure 1:

In the first panel **(A)** is the baseline electrocardiogram (ECG) of the patient with sinus rhythm, right bundle branch block, and 1:1 atrio-ventricular (AV) conduction. **B)** Shows the predischarge control ECG with unipolar stimulation and His capture, with normal intraventricular conduction (narrow QRS), and the chest film **(C)** showing the position of both electrodes prior to discharge. Note that the His electrode was located in the interatrial septum.

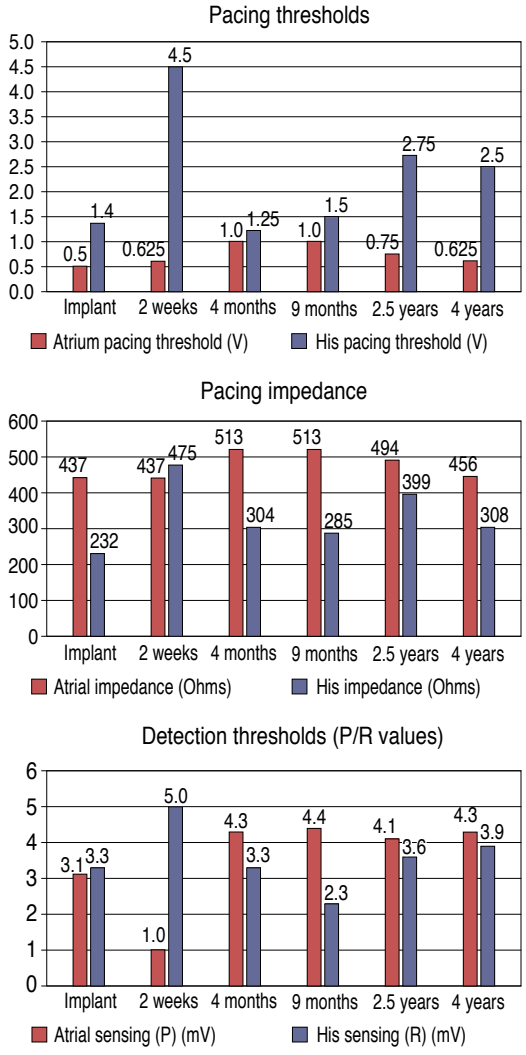

Figure 2: The different graphs show the chronic behavior of several electric parameters of the pacemaker: pacing threshold (volts), pacing impedance (Ohms), and detection thresholds (millivolts) during a four-year follow up.

NYHA functional class I, without any further syncope episodes since the pacemaker's implant. The ECG showed ventricular stimulation with left bundle branch morphology and a 2.25 V RV threshold with 0.5 ms pulse width. During the tests, it was noticed that when the AV-delay is shortened by 20 ms, there is selective capture by His bundle or, at least, a shortening of the QRS duration, so the PM was programmed according to these new findings *(Figure 3)*. During follow-up, no new electrolyte disturbances were identified. Serum creatinine levels returned to normal values after the first interventions and have remained so far within normal limits. She had a complement (C3 and C4) determination in 2020 that was within normal ranges. The only parameter that has consistently remained within 13 and 12.5 mg/dL is the hemoglobin determination.

DISCUSSION

To our knowledge, this is the first reported case of SLE with a high degree of AVB and His stimulation. At the present moment, the patient would be a more suitable candidate for selective left bundle branch stimulation, but at the time of implant, it was not available. We ought to offer her a physiological stimulation mode that would not compromise ventricular function since high stimulation requirements were anticipated.

Rheumatologic disease poses a complex context: inflammation might affect many organs and structures with variable intensity and at different moments. Many times, inflammation may go unnoticed for long periods. The immunologic modulation treatments may also exert some effects on the clinical presentation or lack of presentation of symptoms.

Several mechanisms for cardiovascular involvement have been proposed, including type 1 interferon pathway (IFN-1, IFNα, and IFNβ), autoantibodies, CD16 monocytes, Th17 cells, and low-density granulocyte-mediated damage.[4] Usual cardiovascular risk factors (diabetes, hypertension, dyslipidemia, obesity) also promote atherosclerotic plaque formation and endothelial dysfunction, which are responsible for the main cardiovascular manifestations of SLE.[1] Several risk scores have been developed (Urowitz, Petri, QRISK3), but they focus on ischemic heart disease detection since SLE itself and its treatment promote atherosclerosis and pro-coagulant states instead of rhythm disturbances. It is also known that SLE increases cardiovascular risk by two to 10-fold compared to the general population.[1,3,5]

The incidence of atrio-ventricular conduction disturbances is low in SLE patients.

A report by Natsheh et al. from 2019 mentioned their case and 31 more.[6] The mechanisms are not well understood but seem to be associated with a positive ribonucleoprotein (RNP) antibody.[7] Other actors might be the anti-SSA and anti-SSB antibodies, which might also explain congenital AV-block.[8-10] It is clear that complex immune interactions must play a role, and etiologies other than atherosclerosis or myocarditis must be explored, including the immune-mediated effects on autonomic regulation.

In the present case, since the PM implant, the patient has shown a satisfactory functional class and has had no syncope recurrence. Nonetheless, the stimulation thresholds have changed, and the RBBB has become apparent again unless a fine-tuning of the stimulation parameters (AV-delay, stimulation polarity, His output) achieves a selective capture pattern.

Similar behavior was documented in a case presented by Kishihara J et al.[10] in an SLE patient with conventional ventricular stimulation. They suggest an anatomic-functional interaction: a shorter right ventricular filling interval might lead to different RV dimensions. This will induce discrete modifications in the contact between the lead and the myocardium and a probable accumulation of fluid around the electrode tip that can modify the impedance. The present case showed significant differences in impedance in the first year of stimulation simultaneously with automatic pacing output adjustments. In another case report, a patient without autoimmune disease, a 2:1 AV-block, and His stimulation had a transient increase in the pacing threshold.[11] During follow-up, he presented atrial fibrillation and was started on amiodarone, which was deemed responsible for the increased pacing threshold. The patient, in this case, did not receive any threshold-modifying drugs (mainly antiarrhythmic),[12] so the changes observed are possibly attributable to SLE itself, either from an inflammatory nature or secondary to the fluid accumulation around the tip of the electrode as described by Kishihara. There is scarce information about a direct pro-arrhythmic mechanism linked to SLE, but work by Pisoni C. et al.[13] suggests that positive anti-Ro/SSA antibodies and high IL-1β can modulate cardiac ion channel function and induce prolonged corrected (QTc) interval.

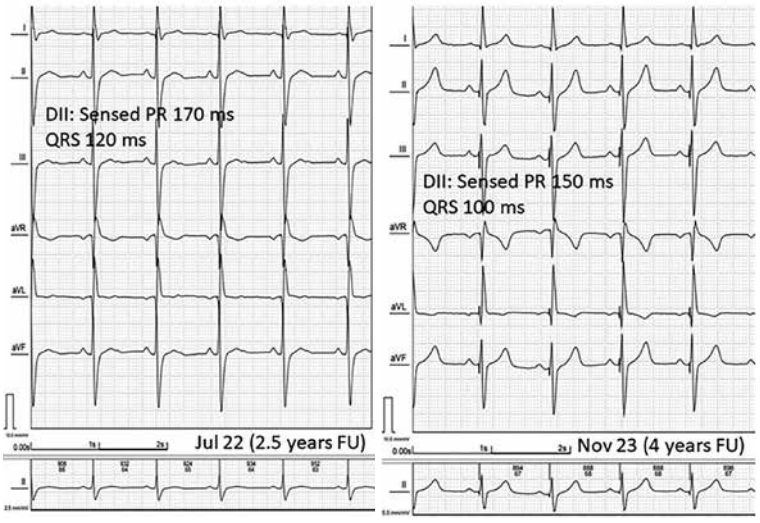

Figure 3: Electrocardiogram (ECG) from one of the latest follow-up visits where the adjustments in the atrio-ventricular (AV) delay show changes in QRS duration when near-selective pacing capture is reached.

CONCLUSIONS

We present here a patient with SLE and His bundle pacing with important variations in stimulation thresholds that forced frequent output, AV-delay duration, and polarity programming changes during a four-year follow-up. Because of the little experience with the matter, many conjectures arise, but it seems apparent that the impedance and threshold behavior when pacing His bundle are not different from pacing other right ventricular areas in SLE. Close monitoring of these rare patients is warranted to evaluate the pacemaker's performance and safety as well as the expected device's longevity. Special attention must be given to the optimal AV delay programming for selective His stimulation. This case could add to the current tendency to prefer left bundle branch pacing over His' stimulation in patients with similar conditions or other rheumatologic diseases.

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Fe de erratas

En el Volumen 35, Suplemento 2, Año 2024, páginas s66 y s256, de la revista *Cardiovascular and Metabolic Science*, se publicó dentro de la sección *3. Cardiología en grupos especiales el resumen 3.3. NT-proBNP como marcador de progresión en pacientes con síndrome cardiorrenal tipo II,* en el cual el nombre del segundo autor dice «Trelles-Hernández Daniel» y debe decir «Trelles-Hernández Daniela».