CASE PRESENTATION

Pyridostigmine induced atrioventricular block in a patient with myasthenia gravis treated with permanent His bundle pacing

Catalin Pestrea[1], Alexandra Gherghina[1], Ramona Magdo-Mina[1], Florin Ortan[1]

Abstract: Myasthenia gravis (MG) is an autoimmune neuromuscular disease, characterized by specific autoantibodies directed against postsynaptic acetylcholine receptors. Although the disease affects primarily the skeletal muscles, involvement of other organs, including the heart, has been noted. The most common cardiac manifestations reported in MG are myocarditis and arrhythmias. The first line treatment consists in acetylcholinesterase inhibitors, of which pyridostigmine is the most effective. They increase the amount of acetylcholine at the neuromuscular junction. This results in an enhanced vagomimetic activity which may lead to serious bradyarrhythmias, including atrioventricular (AV) block. We present the case of a 60-years old patient with known myasthenia gravis under pyridostigmine treatment, which was admitted to our hospital for fatigue and dizziness. The presenting ECG showed sinus rhythm with 2:1 atrioventricular block. We interpreted the case as a symptomatic AV block induced by pyridostigmine at a dose necessary to control the myasthenia gravis symptoms and we decided to implant a permanent dual chamber cardiac pacemaker. In order to minimize the complications associated with long-term ventricular pacing, we opted for permanent His bundle pacing which resulted in atrioventricular resynchronization with normal ventricular electrical activation. The six months follow-up showed optimal stable pacing and sensing parameters and no decline in ejection fraction.
Keywords: myasthenia gravis, pyridostigmine, AV block, His bundle pacing.

Rezumat: Miastenia gravis (MG) este o boală neuromusculară autoimună, caracterizată de prezența unor autoanticorpi împotriva receptorilor colinergici postsinaptici. Boala afectează în primul rând musculatura scheletală, însă atingerea altor organe, inclusiv inima, a fost raportată. Cele mai frecvente manifestări cardiace în MG sunt miocardita și tulburările de ritm. Principalul tratament sunt inhibitorii de acetilcolinesterază, dintre care piridostigmina este cea mai eficientă. Aceștia cresc cantitatea de acetilcolină la nivelul joncțiunii neuromusculare. Astfel, poate apărea un efect vagomimetic susținut, ce poate conduce la bradidisritmii severe, inclusiv bloc atrioventricular. Prezentăm cazul unui pacient în varstă de 60 de ani, cunoscut cu MG sub tratament cu piridostigmină, internat pentru ameţeli și astenie fizică. Electrocardiograma de la internare a evidențiat un bloc atrioventricular grad II 2:1, interpretat ca fiind secundar tratamentului cu piridostigmină în doza necesară pentru a controla simptomele miasteniei. S-a decis cardiostimularea permanentă bicamerală. Pentru a minimiza efectele cardiostimulării electrice pe termen lung, s-a optat pentru stimularea permanentă a fasciculului His, astfel obținându-se resincronizarea atrioventriculară cu menținerea activării electrice normale a ambilor ventriculi. Controlul de șase luni a evidențiat parametri optimi și stabili de pacing și detecție, fără a se înregistra scăderea fracției de ejecție.
Cuvinte cheie: miastenia gravis, piridostigmina, bloc AV, stimulare permanentă a fasciculului His.

INTRODUCTION

Myasthenia gravis is an autoimmune neuromuscular disease that affects primarily skeletal muscles, but in some cases both the disease and the treatment could involve the heart leading to serious complications like myocarditis and rhythm disturbances.

CASE REPORT

A 60 years old patient with known myasthenia gravis under pyridostigmine treatment was admitted to our hospital for fatigue and dizziness. The presenting ECG showed sinus rhythm with 2:1 atrioventricular (AV) block (Figure 1).

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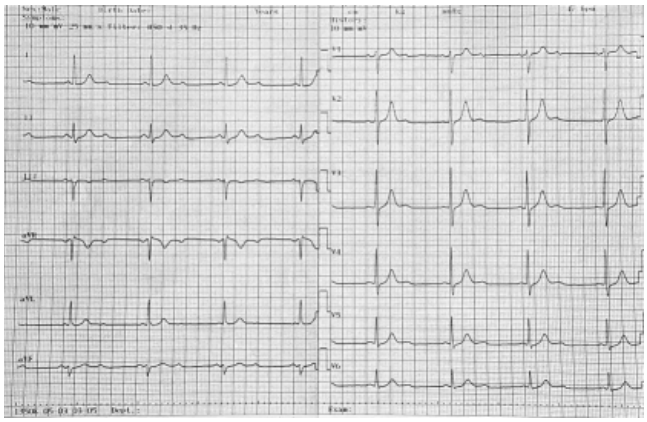

Figure 1. ECG at presentation showing sinus rhythm with 2:1 AV block.

The lab tests were unremarkable and the echocardiography showed normal contractility and a mild mitral regurgitation.

The patient has recently increased the pyridostigmine dose from 15 mg bid to 30 mg bid due to diplopia occurrence and was at that moment asymptomatic in regard to myasthenia gravis.

We interpreted the case as a symptomatic 2:1 AV block induced by pyridostigmine at a dose necessary to control the myasthenia gravis symptoms and we decided to implant a permanent dual chamber cardiac pacemaker.

In order to minimize the complications associated with long-term ventricular pacing, we opted for permanent His bundle pacing.

This procedure has been widely described elsewhere[1]. Briefly, after gaining venous access, with the support of the C315 His sheath (Medtronic, Minneapolis) to reach the septal AV junction, we used the 3830 Select Secure lead (Medtronic, Minneapolis) to map for the His signal and when a good His signal was recorded (Figure 2), the lead was screwed in at that site (Figure 3). A selective His bundle capture was achieved with a threshold of 1 V/1 ms and a sensing value of 3 mV. Finally, an atrial lead was placed in the right atrial appendage.

The post-procedural ECG showed sinus rhythm with atrial synchronized paced QRS complexes with a morphology identical to the native ones (Figure 4).

The patient was discharged the next day. The 1 month, 3 months and 6 months follow-ups showed stable pacing and sensing thresholds (1 V/1 ms and 3 mV respectively), the patient being completely asymptomatic with good exercise tolerance.

DISCUSSION

Myasthenia gravis (MG) is an autoimmune disease in which autoantibodies directed against postsynaptic acetylcholine receptors cause defective neuromuscu-

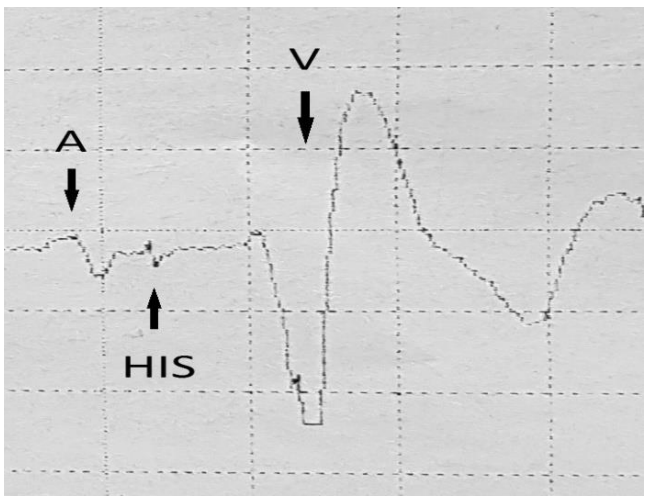

Figure 2. Intracardiac electrogram during mapping showing a good His bundle signal. (A=atrial electrogram; HIS=His bundle electrogram, V=ventricular electrogram).

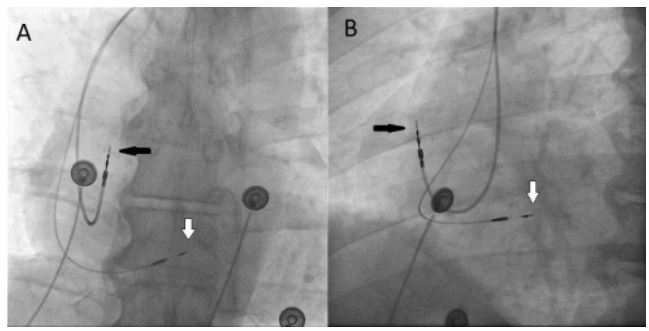

Figure 3. Posteroanterior (A) and left anterior oblique (B) chest x-ray images showing final lead position (black arrow – atrial lead; white arrow – His bundle lead).

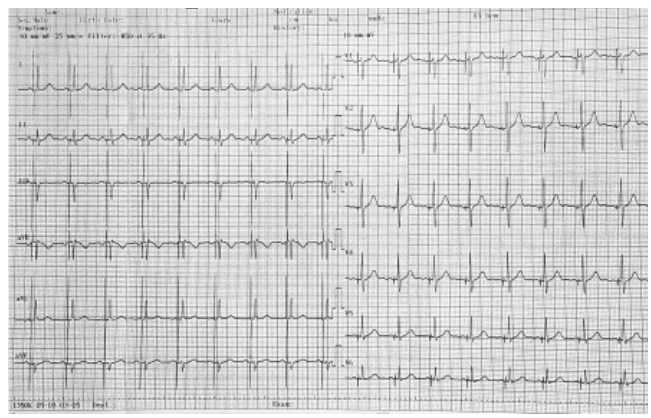

Figure 4. Postprocedural ECG showing selective His bundle pacing: sinus rhythm with atrial synchronized paced QRS complexes with a morphology identical to the native ones.

lar signal transmission, thus resulting in skeletal muscle weakness[2].

Although the disease affects primarily the skeletal muscles, involvement of other organs, including the heart has been noted.

The most common cardiac manifestations reported in MG are myocarditis and arrhythmias[3].

Antibodies against acetylcholine receptors do not bind to myocytes. On the other hand, striational antibodies (anti-titin, anti-ryanodine receptor and anti Kv 1.4 antibodies) attack the heart muscle and this appears to be the cause of myocardial inflammation[4].

Also, the presence of thymoma associated with MG was shown to be an important prognostic factor for myocarditis because 97% of these patients have striational antibodies[5].

So far, no definite direct effect of MG on the cardiac conduction system could be determined.

Apparently, most of the fluctuations in heart rate are due to autonomic imbalance[6]. But, in patients with anti Kv 1.4 antibodies, more serious arrhythmias like ventricular tachycardias, complete AV block and sudden cardiac death have been described.

One of the mainstays of MG treatment are acetylcholinesterase inhibitors, of which pyridostigmine is the most effective. The mechanism of action is an increase of acetylcholine concentrations at the neuromuscular junction and thus an increased acetylcholine receptor stimulation[7].

This results in an enhanced vagomimetic activity which could lead to bradycardia or AV block, because the AV node is richly innervated with cholinergic neurons.

Although acute electrophysiological studies showed no significant prolongation of AV node conduction after pyridostigmine administration[8], there are several case reports in the literature describing either sinoatrial or AV block leading to hospitalization and even cardiac pacing in patients receiving this treatment[9,10].

In our case, the patient had no thymoma and his AV conduction abnormalities appeared after the increase in pyridostigmine dose for diplopia.

For these reasons, we interpreted the case as a drug related symptomatic second degree AV block and because we didn't want to withdraw the medication due to concern of MG symptoms relapse, we decided to implant a permanent dual chamber pacemaker.

When considering permanent cardiac pacing, a careful balance must be made between the benefits of atrioventricular resynchronization and the deleterious effects of long term right ventricular pacing.

One of the most serious adverse effects of a high right ventricular pacing burden (especially more than 40% of the time) is a decrease in left ventricular systolic function, the so called pacing induced cardiomyopathy. This is usually defined as a drop in ejection fraction of more than 10% resulting in a value below 50% and it is encountered in approximately 20% of the paced patients[11].

Another potential problem associated with the presence of a right ventricle lead is an increase in tricuspid valve dysfunction, which could lead in time to right heart failure and systemic congestion[12].

Fortunately, in the last decade, to overcome these issues, new forms of physiological pacing have been studied and His bundle pacing emerged as the most physiological one.

The advantages of this kind of cardiac pacing are obvious – the electrical activation of both ventricles is synchronous because it uses the intrinsic conduction system and usually the lead is placed on the atrial side of the tricuspid valve (Figure 5), which prevents tricuspid regurgitation worsening.

Therefore, using a dual chamber pacemaker, one can achieve atrioventricular resynchronization, thus fully optimizing ventricular filling and the cardiac output, without the long term deleterious effect of right ventricular pacing[13].

With the recent advances in technology and the latest lead delivery systems, a success rate of up to 90% in His bundle pacing has been demonstrated with little adverse effects[14].

Depending on the QRS morphology, after His bundle pacing, two types of response have been described: selective His bundle pacing, in which there is

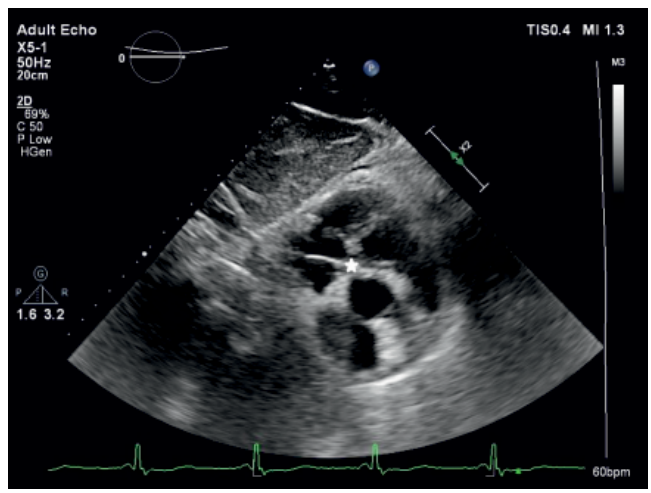

Figure 5. Subcostal short-axis view echocardiography image showing His bundle lead tip fixed on the atrial side of the tricuspid valve (white star).

only His bundle capture and the resulting QRS and T wave are identical to the native ones and non-selective His bundle pacing, in which there is both local capture in the basal septal myocardium and His bundle capture with a resulting narrow QRS with a "pseudo delta wave" appearance and a modified T wave[15].

There are several studies which show no significant hemodynamic differences between the two responses[16].

Several potential issues with His bundle pacing could occur, like an increasing pacing threshold, atrial oversensing and ventricular undersensing.

In our case, we achieved selective His bundle pacing at a low threshold (1 V/1 ms) and with decent sensitivity (3 mV), which remained stable over time.

Although the patient was 100% ventricular paced, there was no decrease in systolic function at follow-up.

In this way, we were able to keep the necessary doses of pyridostigmine to control the myasthenia gravis symptoms while maintaining the normal electrical activation of the heart.

CONCLUSION

In this subset of patients with drug-related bradyarrhythmias, His bundle pacing is an option to effectively restore the normal electrical cardiac activation, while continuing the necessary medical treatment.

Conflict of interest: none declared.

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