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Pyridostigmine-induced high grade SA-block in a patient with myasthenia gravis

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Patient: Female, 70
Final Diagnosis: SA block induced by pyridostigmine
Symptoms: Asymptomatic
Medication: Pyridostigmine
Clinical Procedure: Pacemaker insertion
Specialty: Electrophysiology

Objective: Unusual clinical course

Background: Myasthenia gravis requires a long-term treatment with a parasympathomimetic agent, which may result in bradycardia and asystole. Pharmacologic treatment with a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) and Methylprednisolone is seen to improve the muscular symptoms but may reinforce potential bradyarrhythmias. This potential side effect can be treated with the levo isomer of atropine, Hyoscyamine, or Glycopyrollate in an intact conduction system.

Case Report: A 70-year old Caucasian female patient with a family history of myasthenia gravis presented with mild weakness of the bilateral facial muscles, moderate dysarthria, dysphagia, diplopia predominantly on the right side and difficulty tracking ocular movements bilaterally. The treatment with pharmacological agents was initiated. Subsequently she developed asymptomatic bradycardia and SA-block. An improvement on Hyoscyamine failed to appear. A dual chamber pacemaker was placed.

Conclusions: In symptomatic or asymptomatic bradycardia with significant high grade SA-block in patients with myasthenia gravis the insertion of a permanent pacemaker can be the definitive solution.

Key words: SA block • pyridostigmine induced bradycardia • myasthenia gravis

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Background

Myasthenia gravis is an autoimmune neuromuscular disease that causes muscle weakness and fatigability with increased activity. The circulating antibodies block nicotinic acetylcholine receptors at the postsynaptic neuromuscular junction [1] causing an inhibitory effect.

Myasthenia gravis is treated medically with acetylcholinesterase inhibitors and/or immunosuppressants, and with thymectomy especially in patients with thymoma. Bradyarrythmias have been reported in patients treated with Acetylcholine esterase inhibitors for myasthenia gravis [2].

We present a case of a 70-year-old Caucasian female with myasthenia gravis, who developed bradycardia and significant SA-block with the initiation of pyridostigmine.

Case Report

Seventy-year-old Caucasian female without significant past medical history presented with 3-year history of weakness, diplopia, dysphagia and fatigue. She reported a family history of Myasthenia Gravis (MG) affecting her mother and two brothers.

Physical examination revealed bilateral facial paresis, moderate dysarthria, dysphagia and diplopia. Muscle strength was 3/5 in the lower extremities without involvement of the upper extremities. The sensory and sphincter function were intact. Reflexes were normal.

Taking the family history into consideration an ice-pack-test was performed on the admission's day. However the patient did not have clear ptosis and the test was not significant enough. Diagnostic steps were advanced to the tensilon test using 4 doses of 1 mL of edrophonium, 60 seconds apart, on this patient with rapid improvement after the infusion of the drug, which was observed in the diplopia and jaw weakness. Acetylcholine receptor antibodies (AChR-Ab) and MuSK-protein antibodies were detected. TSH-level was normal; other laboratory workup was not significant.

Repetitive nerve stimulation test was performed. Low-rate-stimulation-waves of 2 Hz in up to 8 consecutive stimulations were applied to the facial/ perioral muscles. The patient was asked to talk for 30 seconds after the 1st stimulation-wave-application followed by 6 more stimulation waves at 2 Hz. Subsequently the patient was barely able to talk after the test.

With these serological and electrophysiological findings the diagnosis of MG was confirmed. Thymoma was excluded radiologically.

Pharmacologic treatment with pyridostigmine 30 mg orally Q 4 hrs and methylprednisolone 1000mg daily was initiated. The clinical symptoms began to improve after the third day. On the 4th/5th day, the patient developed an asymptomatic bradycardia and 5.9 second asystole consistent with the diagnosis of SA-block.

To further avoid in increase in the pyridostigmine dose the treatment the addition of mycophenolate mofetil was discussed. However due to it's delayed onset of action in relation to the subacute developed bradycardia mycophenolate mofetil was not given. In contrast glycopyrrolate was added to counteract the pyridostigmine side effects; however, it did not improve the bradycardia. To minimize the acute complications and to counteract the progressive pyridostigmine-induced bradycardia, although no myasthenic crisis was observed, a five-day-course of IVIG (IgG) 400 mg/kg daily was given. Additionally Hyoscyamine 0.125 mg was initiated.

Cardiac catheterization was performed in the 8th day of hospitalization to rule out possible cardiac origin of the arrhythmia. These were reported to be normal.

Despite these measures significant bradycardia and pauses continued (Figure 1). A dual chamber permanent pacemaker was implanted on eleventh day and pyridostigmine dose was increased. Neurologic symptoms continued to improve.

Discussion

Myasthenia gravis is an autoimmune neuromuscular disorder with generalized muscle involvement resulting in weakness and fatigue [2]. The incidence is approximately 1:40000 per year with maximum prevalence in the 3rd and 4th decade in women and in the fifth decade in men [3]. There is a slight genetic predisposition associated with different HLA types. About 60-70% of the patients have an abnormality of the thymus and 20% have a thymoma [4].

The main stay in myasthenia gravis treatment is acetylcholinesterase-inhibitors and/or immunosuppressants, and with thymectomy in patients with thymoma. Bradyarrythmias have been reported in patients treated with Acetylcholine-esterase-inhibitors [1,2].

The association between myasthenia gravis and cardiovascular diseases has been known for many years, but no specific etiologic link has been established. Most of the data have been derived from either case series or case reports [3].

Guglin et al. have shown cardiac involvement in patients with myasthenia gravis [4]. In 16% atrial fibrillation, atrioventricular blocks, asystole, and sudden death were attributed to possible

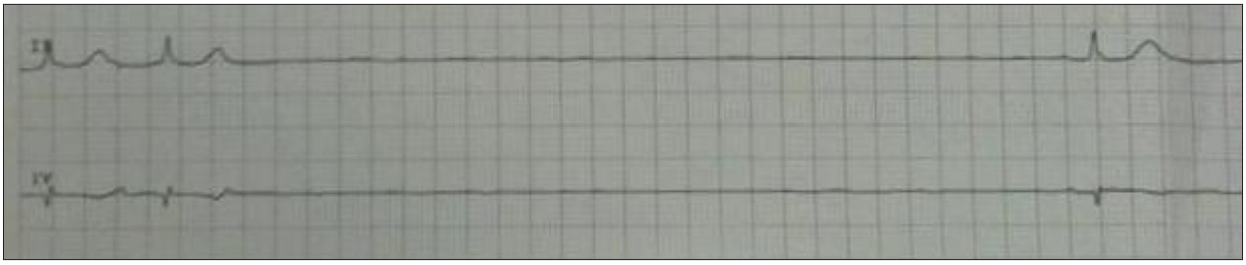

Figure 1. Telemetry tracings on the 5th day of the hospitalization showing SA-block of 5.9 seconds.

myocarditis from the autoimmune involvement. Cardiovascular involvement occurred more in patients with thymoma (50%), compared to those without thymoma (12%). Arrhythmias were common clinical manifestation and these patients were noted to be at an increased risk of sudden death. However, some of the patients in these studies were not tested for coronary artery disease; their EKG changes could not be attributed to cardiac involvement due to myasthenia gravis.

In 2008 Gehi et al. [5] reported case of myasthenia gravis with pyridostigmine-induced high grade AV-block and recurrent episodes of syncope. This patient was subsequently treated with hyoscyamine, the AV-block disappeared completely without further syncope, and therefore a permanent pacemaker was avoided. However, our patient, despite therapy with hyoscyamine, continued to have significant pauses thus requiring permanent pacemaker.

Immunoglobuline (IVIG) and/or plasmapharesis are frequently used to reverse an exacerbation of myasthenia gravis. The effect of IVIG is seen in less than a week and the benefit can last for few weeks. However limited data for the effectiveness of IVIG for myasthenia gravis without crisis are available [6,7].

Following a similar presentation from a case report the addition of IVIG in our patient was a part of the treatment. In this reported case in 2004 Hemender et al. [8] treated a patient with atrioventricular block induced by myasthenia gravis, resulting in a favorable course, with immunosuppressive therapy and plasmapheresis.

To our knowledge, pyridostigmine-induced high grade AV-block has been reported, yet pyridostigmine SA-exit block and sinus-arrest-block resulting in prolonged pauses in a patient with myasthenia gravis has not been reported previously.

Conclusions

It is possible that the same autoimmune process that causes myasthenia gravis also affects the SA-node resulting in clinical manifestation of sick-sinus-syndrome and this effect might be aggravated by the use of pyridostigmine as in our patient. Nonetheless, pyridostigmine as a significant part of the myasthenia gravis therapy can be continued after the insertion of a permanent pacemaker, if that complication was to occur.

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