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CASE PRESENTATION

Iatrogenic cholinergic syndrome in the treatment of myasthenia gravis: a case report

Síndrome colinérgico iatrogénico en el tratamiento de la miastenia gravis: reporte de un caso

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ABSTRACT

Introduction: cholinergic syndrome encompasses a set of symptoms and signs caused by an excess of acetylcholine or exogenous substances that stimulate the Parasympathetic Nervous System. It may be caused by overdose of cholinergic drugs such as pyridostigmine.

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Objective: to present the case of a patient with iatrogenic cholinergic syndrome in the treatment of myasthenia gravis.

Case Presentation: a 22-year-old male patient with a history of myasthenia gravis is presented, who arrived at the emergency room suffering from chest pain predominantly in the left hemithorax, profuse sweating, paleness, coldness, extreme bradycardia and arterial hypotension. After the interrogation, it was learned that he was taking pyridostigmine, an anticholinesterase drug to treat his underlying illness. His doctor had prescribed an increase in the dose because he was decompensated, which probably triggered the cholinergic syndrome.

Conclusions: the case is presented due to the importance of early identification of muscarinic and nicotinic signs and symptoms, added to the need to promptly correct possible complications that could lead the patient to a fatal outcome.

Keywords: Acetylcholine; Atropine; Cholinergics; Myasthenia gravis

RESUMEN

Introducción: el síndrome colinérgico engloba un conjunto de síntomas y signos provocados por un exceso de acetilcolina o sustancias exógenas que estimulan el Sistema Nervioso Parasimpático. Puede estar causado por sobredosis de fármacos colinérgicos como la piridostigmina.

Objetivo: presentar el caso de un paciente con síndrome colinérgico iatrogénico en el tratamiento de la miastenia gravis.

Presentación del Caso: se presenta paciente masculino de 22 años con antecedentes de miastenia gravis, que llegó al cuerpo de guardia aquejado de dolor torácico con predominio en el hemitórax izquierdo, sudoraciones profusas, palidez, frialdad, bradicardia extrema e hipotensión arterial. Tras el interrogatorio se supo que se medicaba con piridostigmina, medicamento anticolinesterásico para tratar su enfermedad de base. Su médico le había prescrito un incremento de la dosis por encontrarse descompensado, lo que probablemente desencadenó el síndrome colinérgico.

Conclusiones: se presenta el caso por la importancia de la identificación temprana de los signos y síntomas muscarínicos y nicotínicos, sumado a la necesidad de corregir oportunamente posibles complicaciones que pudieran llevar al paciente a un desenlace fatal.

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Palabras claves: Acetilcolina; Atropina; Colinérgicos; Miastenia Gravis

INTRODUCTION

Cholinergic syndrome encompasses a set of symptoms and signs caused by excess acetylcholine. This is the main neurotransmitter of all preganglionic endings of the vegetative system, as well as postganglionic nerve fibers. It acts through nicotinic cholinergic receptors (in the autonomic ganglia, motor plate, adrenal medulla and central nervous system) and muscarinic receptors (central nervous system and target organs). It undergoes continuous inactivation by anticholinesterases. Inhibition of the activity of this enzyme causes cholinergic syndrome: excess acetylcholine causes a state of prolonged depolarization of the postsynaptic membranes, which prevents the conduction of the stimulus. [1,2]

It may be caused by overdose of cholinergic drugs such as pyridostigmine or pilocarpine. Pyridostigmine is a cholinesterase inhibitor and its effects are to compete with acetylcholine for its acetylcholinesterase binding site. By interfering with the enzymatic destruction of acetylcholine, the cholinergic action is enhanced, both in the skeletal muscle (nicotinic receptor) and the gastrointestinal tract (muscarinic receptor). [3] It is the most widely used agent of the group for the oral treatment of myasthenia gravis.

Myasthenia gravis is an autoimmune disease characterized by fatigue and predominantly proximal muscle weakness (eye muscles, bulbar functions of the extremities and respiratory muscles). It can manifest at any age. The onset can be insidious, almost always related to a predisposing factor such as stress or physical/emotional trauma. [4]

Regarding the case in question, there are few references or similar records, so the objective was to present the case of a patient with iatrogenic cholinergic syndrome in the treatment of myasthenia gravis and thus characterize its clinical symptoms, symptoms and evolution, which would help to better understand its form of presentation and etiopathogenesis.

CASE PRESENTATION

A 22-year-old black male patient with a personal medical history of myasthenia gravis (diagnosed six months ago), for which he is receiving stable treatment with pyridostigmine. For the last month he has been experiencing fatigue, drooping of the eyelids, muscle weakness and salivation. He arrives at the emergency room suffering from chest pain predominantly in the left

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hemithorax, accompanied by profuse sweating, paleness, coldness, extreme bradycardia and arterial hypotension. It was decided to admit him to the Intensive Care Unit (ICU) of the General Teaching Hospital "Dr. Mario Muñoz Monroy" from Colón, in the province of Matanzas, with an initial presumptive diagnosis of a cholinergic syndrome due to pyridostigmine overdose.

Physical Examination (Positive):

Long-line patient with difficulty walking, myasthenic facie, divergent strabismus, rapid muscle fatigue due to repetitive and prolonged movement, miosis, tearing, pale skin - cold and sweaty -, moist and normal-colored mucous membranes, without edema in the lower limbs. Respiratory System: normal chest expansion, audible breath sounds, RR 24xmin. Cardiovascular System: bradyarrhythmic heart sounds (30 beats per minute), arterial hypotension (60\40 mm/Hg). Central Nervous System: drowsy, responds to moderate intensity stimuli, isochoric pupils reactive to light and generalized weakness.

Complementary Exams

Leukogram: normal; Erythrocyte sedimentation rate: accelerated; Blood glucose: 1,0 mmol\L (hypoglycemia); Hematocrit: 0,45 % (normal); Creatinine: 90 µmol\L (normal).

Gasometry and Ionogram: Ph: 7,39; PCO2: 45; PO2: 81; SO2: 94,2; K: 3,1; Na: 140; BE: 2,7; HCO3: 26,3 (metabolic acidosis). Chest X-ray: no alterations. Electrocardiogram (Figure 1).

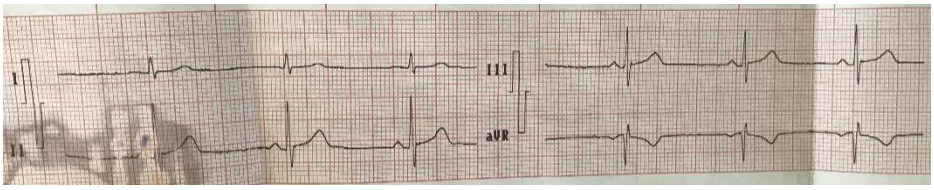

Figure 1. Electrocardiogram showing the patient's bradycardia.

Syndromic Approach: Cholinergic syndrome.

Nosological Approach: Pyridostigmine poisoning.

Diagnostic Impression: Cholinergic crisis.

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DISCUSSION

Remijn Nelissen et al., [4] state that the characteristics of myasthenia gravis vary depending on the part of the world and its prevalence is between 0.5 and 20.4 cases per 100,000 inhabitants, with an annual incidence of 0,3 per 100,000 inhabitants. Alhaidar et al., [5] comment that it constitutes a disorder of neuromuscular transmission, due to an autoimmune decrease in the number of acetylcholine receptors in the motor plate. Therefore, its treatment consists of the administration of anticholinesterases such as pyridostigmine, which by increasing the availability of acetylcholine favors neuromuscular transmission.

This drug is the one that causes the least adverse reactions within its family, leaving organophosphates as the main incident of the cholinergic crisis. A study on cholinesterase levels for the diagnosis of intoxication or poisoning by organophosphate and carbamate pesticides, as well as its potential application in forensic toxicology, demonstrated the proven practical usefulness of cholinesterase levels, concluding that the most frequent poisonings that reach the emergency service are for agricultural products. [5,6]

Cholinergic crisis (rare) consists of an increase in weakness, produced by the administration of an excessive dose of an anticholinesterase. The trigger for the symptoms that led to admission could have been an excess dose of pyridostigmine, which probably evolved into a cholinergic syndrome with muscarinic manifestations (miosis, blurred vision, hypersalivation, respiratory distress, lacrimation, diaphoresis, bradycardia and urinary incontinence) and nicotinic (muscle weakness, headache, cramp, hypoglycemia and paleness). [6]

It is not uncommon to find both muscarinic and nicotinic symptoms and signs simultaneously. There may be mydriasis, miosis, and even normal pupils. Fasciculations and weakness are considered by some to be the most reliable findings in this type of poisoning. Classically, the mnemonics DUMBELLS (diarrhea, urination, miosis, bradycardia, emesis, lacrimation, lethargy and salivation) and SLUDGE (salivation, lacrimation, urination, defecation, gastrointestinal upset, emesis) are mentioned as representing the most common signs. But, although nausea and vomiting are common, diarrhea and relaxation of the urinary sphincter are uncommon. [6]

Clinical findings suggestive of severity are: changes in mental status, coma, seizures, bronchorrhea, severe respiratory distress, bronchoconstriction, fasciculations, severe generalized weakness, involuntary defecation,

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autonomic instability and paralysis. Bronchorrhea can progress to pulmonary edema and respiratory failure. (7)

Hypervagotonia may resemble cholinergic syndrome, but it is short-lived and its symptoms are mild. Pronounced dyspnea associated with bronchorrhea and bronchoconstriction may suggest suspicion of cardiogenic pulmonary edema, toxic injury to the respiratory system due to irritating gases, or status asthmaticus. Muscle weakness may resemble symptoms of myasthenia or pseudomyasthenic crisis. Colic and diarrhea raise suspicion of an acute disease of the digestive tract. (7)

The diagnosis is based on the clinical picture, taking into account the muscarinic and nicotinic signs, especially in the absence of a known history of intake. If the clinical evaluation is suggestive, this diagnosis is considered a fact until proven otherwise. (8)

Laboratory tests are generally normal. However, there are findings that can confuse the diagnosis, so the physical examination and clinical history should prevail. In the electrocardiogram we can find tachycardia or bradycardia, atrioventricular block, prolonged QT and torsades de pointes. Blood tests may reveal ketoacidosis, elevated serum amylase, creatine kinase, and glucose, decreased lipid, decreased or increased potassium, and leukocytosis with left shift, as well as glycosuria and proteinuria. (8,9)

Treatment must be carried out in the intensive care unit. It is necessary to monitor cardiac function and breathing. Atropine is the drug of choice; 1-5 mg should be injected intravenously and repeat the dose every few minutes until the amount of bronchial secretions and dyspnea reduce. During rapid atropinization, respiratory paralysis or excessive secretions should be managed by intubation, ventilation, and continuous suctioning. (9)

As a maintenance guideline, it is established that, if the required hourly dose is high, atropine should be administered in continuous infusion, dissolved in physiological saline, and maintained as long as muscarinic symptoms persist. It should be suspended if complete atropinization occurs (mydriasis, delirium, hallucinations, tachycardia greater than 120 l/min), with greater caution in the case of the elderly, thyrotoxicosis, ischemic heart disease and previous arrhythmias. (10)

The dosage should be established so that it is not necessary to aspirate excess bronchial secretions more frequently than once per hour.

CONCLUSIONS

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The management of these patients, regardless of the cause that caused the cholinergic syndrome, consists of reversing the effect of the inhibited cholinesterase (which has produced a series of negative effects as a result of an excess in the dose of the medication). Medical care should be carried out as soon as the first symptoms appear, in order to avoid complications that endanger the patient's life.

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AUTHORSHIP CONTRIBUTION

YNG: Conceptualization, data curation, formal analysis, research, visualization, writing - original draft, writing - review and editing.

LLFB: Conceptualization, formal analysis, research, writing - original draft.

IGL: Conceptualization, formal analysis, research, writing - original draft.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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