PAROXYSMAL SYMPATHETIC HYPERACTIVITY FOLLOWING CARDIAC ARREST DUE TO MASSIVE PULMONARY EMBOLISM: A CASE REPORT

HIPERATIVIDADE SIMPÁTICA PAROXÍSTICA APÓS PARADA CARDÍACA POR EMBOLIA PULMONAR MACIÇA: UM RELATO DE CASO

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ABSTRACT
Paroxysmal sympathetic hyperactivity (PSH) manifests with episodes of autonomic dysregulation including hyperthermia, diaphoresis, tachypnea, tachycardia, hypertension, and dystonic posture. Its differential diagnosis is made with several more prevalent pathologies, which can cause a delay in the diagnosis, making knowledge of this disease very important. Herein, we report the case of a patient who was diagnosed with PSH following cardiac arrest and discuss briefly the pathophysiology, clinical presentation, and management of this clinical entity.

Keywords: Neurology; Dystonia; Biperiden; Movement disorders.

INTRODUCTION

Initially known as diencephalic seizures and sympathetic storms, paroxysmal sympathetic hyperactivity syndrome (PSH) was first described by Penfield in 1929. Is characterized by paroxysms of pronounced origin, diaphoresis, hyperthermia, hypertension, tachycardia and tachypnea accompanied by hypertonia and extensor tendency (1, 2, 3). It manifests itself mainly in the intensive care environment, but it can persist for months during a patient's rehabilitation phase (2,3). The early recognition of this syndrome is important, due to its impact on morbidity, at the time of hospitalization and the clinical impression is that PSH is an independent risk factor for worse neurological outcomes in patients who have suffered brain damage (1, 4). In this report, we will talk about a patient who suffered cardiac arrest due to acute pulmonary embolism (PE), developed this syndrome subsequently, and had a good clinical response after treatment.

CASE PRESENTATION

A healthy 22-year-old male patient was involved in an automobile accident with a fracture of the tibial plateau and right patella, requiring a surgical approach, with good evolution. Twenty-two days later, he developed sudden dyspnea, tachycardia, and cyanosis,

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progressive worsening clinical status, followed by three Pulseless Electrical Activity (PEA) cardiac arrests, after a prolonged Cardio Pulmonary Resuscitation (PCR), he returned to spontaneous circulation and was then referred to our service for tertiary care. On arrival, he was hemodynamically compensated with vasoactive drugs, heavily sedated, his vital signs were as following: blood pressure 168/88 mmHg, heart rate 108 bpm, O2 saturation of 98% on pulse oximetry. On examination, he had bleeding at the venous access site. During the patient's management, he presented epistaxis requiring nasal packing. Head computed tomography (CT), chest CT angiography (CTA), and laboratory tests were ordered. The head CT was unremarkable, the CTA chest showed filling defects suggestive of PE in the lobar and segmental branches of the lower left lobe. Among the abnormal laboratory tests were creatinine 2.13 (Reference Range: 0.70 to 1.20 mg/dL), arterial blood gases: ph 6.74, pO2 89, pCO2 66, bicarbonate 9, SpO2 98%, Prothrombin-time international normalized ratio (PT/INR) 2.1 (RR: 0.82 to 1.17), uncoagulable activated partial thromboplastin time (aPTT), fibrinogen 75 mg/dL (RR: 200 to 393 mg/dL). At that moment, measures were initiated to correct hydroelectrolytic disorders, in addition to cryoprecipitate and fresh plasma transfusions. Due to the active bleeding sites, we chose not to initiate anticoagulation or thrombolysis of acute pulmonary embolism.

In the following days under ICU care, the patient maintained oral bleeding and worsening of renal function (AKIN 3) but without the need for dialysis. Arterial Doppler Ultrasonography of the lower limb arteries revealed subacute thrombosis in the popliteal artery in the right lower limb, transthoracic echocardiography was unremarkable.

On the fourth day in the ICU, he did not show signs of arousal after withdrawal from sedating drugs, maintaining Glasgow Coma Scale (GCS) of 3, and worsening of the ventilatory pattern and laboratory profile, thus antibiotic therapy was started for ventilator-associated pneumonia; it was also noted dystonic movements in the upper limbs that subdued after Intravenous (IV) diazepam. The patient persists with fever, diaphoresis, tachycardia, unsatisfactory ventilatory pattern and with extensive dystonic movements that worsened the patient's manipulation. Continuous Electroencephalography (EEG) was performed due to the persistence of dystonic movements, which showed severely abnormal background activity with a continuous severe diffuse slowdown, but without inter-ictal and ictal activity, in addition to the evidence of brief tonic movements in limbs without association with changes in the electroencephalographic record. Therefore, on-demand IV diazepam was maintained for symptomatic control and associated morphine for pain and movement control.

On the 10th day of ICU, the patient has improved blood dyscrasia and renal function, a tracheostomy has been performed without complications, a slight improvement in the level of consciousness (GCS 7 – spontaneous eye-opening), but persists with dystonic movements (at times, a similar pattern of decerebrate dystonic movements was noted), diaphoresis, hyperthermia and tachycardic. Another Video-EEG was performed without significant changes, opting to keep diazepam 30 mg / day, morphine 12mg/day and started baclofen 30 mg / day (with gradual increase). An only slight improvement was noted after medication changed, and antibiotic coverage was redirected for bloodstream infection (Staphylococcemia), a transesophageal echocardiography was performed, which did not show intracardiac vegetation.

Days later, the dystonic movements worsened, now including all four limbs. It was especially unnerving to the care team and family members alike. Medications dosage were increased (diazepam to 60mg/day and baclofen 120mg/day), in addition to the gradual start of trihexyphenidyl up to the dose of 60mg/day. The patient continues to progressively improve clinical status, but without likewise improvement in his dystonic movements. At that moment, we chose to start levodopa/benserazide, but the patient had dermatological allergic reactions, and so it was discontinued. Two days later trihexyphenidyl was also discontinued.

About a month after admission, with improved pharmacoderma, as motor symptoms persisted, it was initiated biperiden with gradual increase up to 16mg / day. Patient evolves with significant improvement in movements, occasionally presenting during manipulation. The patient persists well clinically, only with persistent tachycardia, periods of hyperthermia without an infectious focus, and is discharged from the ICU after 37 days.

Dehospitalization process started, patient still with tracheostomy, feeding via SNG and without sphincter control, beginning to show interaction with family members. Due to autonomic instability (persistent tachycardia without apparent cause) propranolol 40mg / day and clonidine 0.300 / day were started, with good symptom control. Warfarin 5mg / day guided according to INR was also started, for the treatment of pulmonary embolism, now that the patient was clinically stable and without active bleeding. Patient is discharged 52 days after admission.

Upon returning to our clinic 30 days after discharge, he presented 1 episode of seizure and started carbamazepine 600mg / day by another team, opting to keep the medication for the moment. Patient undergoing physical therapy treatment with significant improvement in gait, although ataxic, and speech therapist with gradual return of speech. Four months after

discharge, the patient removes a tracheostomy and is dependent for activities of daily living, despite the limitations, he no longer had seizures or dystonic movements. At the return of one year, the patient continues without new seizures, has sporadic myoclonus associated with an emotional trigger, but with a good response to diazepam. Gradual weaning of baclofen was initiated and clonidine was suspended, other medications and non-pharmacological measures were maintained.

DISCUSSION

Paroxysmal sympathetic hyperactivity syndrome (PSH) has been known for many years, however it was only in 2014 that the conceptual definition of PSH was formulated, which defines as “A syndrome recognized in a subset of survivors of severe acquired brain injury, with simultaneous and transient paroxysmal sympathetic increase (high heart rate, blood pressure, respiratory rate, temperature, sweating) and motor activity (posture)” (1,2,5). In some cases, capable of making extreme opisthotone ("cercle arch") (6). The onset of these typical clinical signs usually occurs in the first week after the brain injury and can persist for weeks or months, especially in patients with hypoxic injuries (2,3).

We currently have a Paroxysmal Sympathetic Hyperactivity-Assessment Measure (PSH-AM) scale, which consists of two separate constructs: (1) the clinical characteristics scale (CFS), to identify the intensity of cardinal characteristics, and the probability tool (DLT), to assess the likelihood of the presence of PSH, and is by far the best diagnostic tool for PSH (1, 2). Few patients with PSH have all the characteristics of the syndrome and the longer the time of manifestations, the greater the probability of being PSH (1).

Studies show an association of PSH with severe traumatic brain injury in 80% of cases, other causes include cerebral anoxia, subaraconidic and intracranial hemorrhages and hydrocephalus (4, 7). Furthermore, the risk factors for the development of PSH after acute brain injury include the severity of the initial brain injury, younger age and male gender (8).

Infections, sepsis, pain, opiate withdrawal, neuroleptic malignant syndrome, thyroid storm, malignant hyperthermia and seizures are all diagnoses that have overlapping clinical presentations that need to be excluded from the diagnosis of PSH. Some of these diagnoses can coexist with PSH and, in fact, can trigger episodes that hinder the management and diagnosis of PSH (1,2,3,8). As observed in our patient, who had more than one case of sepsis during hospitalization.

PSH can be caused by different injury mechanisms in different locations, explaining the variability of symptoms and severity. Regardless of the location of the lesion, the common final route is an imbalance in the adrenergic flow (8). An synthesis of this theory (the excitatory:inhibitory ratio model) suggested that the underlying mechanism is a disconnection of the cortical inhibitory centers, such as the insula and cingulate cortex, from the hypothalamic, diencephalic and brainstem centers that are responsible for the supraspinatus control of the sympathetic tone, causing excitation of the spinal circuit; the paroxysms then resolve in response to the recovery of the inhibitory conductors (2, 4, 8).

Regardless of these central neurotransmitter changes, evidence supports an association between PSH and peripheral catecholamines and, possibly, corticosteroid release, which may explain the exaggerated responses to non-harmful or slightly harmful stimuli seen in patients with PSH, some precipitating factors may be manipulation of the endotracheal tube, oropharyngeal bathroom, pain during wound dressing or direct physical injury to the head and bladder distention (4, 9, 10).

Treatment options for PSH are mainly symptomatic. The three main objectives of treating are to avoid the triggers that cause paroxysms, attenuate excessive sympathetic flow and address the effects of PSH on other organ systems through supportive therapy (2, 4). Usually, it is necessary to combine different drugs and non-pharmacological treatment modalities (4, 8). No clear evidence suggests that one medication regimen is superior to another, and drugs seem to work well for some patients but not others (3). Two recent studies have even suggested a flow chart for the management of patients with PSH, based on those same objectives of treating (7, 8).

The studies in the area point to morphine and short-acting benzodiazepines as first-line treatment options due to their effectiveness, and quick action, consequently aborting paroxysms (4, 7, 8). Morphine, beyond pain control, can also have non-analgesic effects, modulating the central pathways involved in paroxysms (4, 8). In general, the duration of opioid therapy depends on the duration and severity of PSH symptoms, but treatment with opioids often extends into the rehabilitation phase. Care should be taken with the removal of the opioid in the rehabilitation phase, due to the risk of triggering new paroxysms (4). Clonazepam, diazepam, and lorazepam are widely used for the treatment of dystonia and spasticity, also have been used with some success in management of symptoms such as tachycardia and hypertension. The effectiveness of benzodiazepine may suggest the interruption of central GABA systems (8, 10).

Symptom preventive drugs should be started to decrease the frequency and intensity of episodes, having to be started concomitantly with symptomatic treatment. These include non-selective blockers, alfa 2 agonists, bromocriptine, baclofen, gabapentin and long-acting benzodiazepines (4, 7, 8). Drugs that cause b-adrenergic block, such as propranolol (non-selective b-adrenergic block) are pertinent choices with proven clinical efficacy for the improvement of sympathetic symptoms (such as hypertension, tachycardia and sweating, some authors report improvement even in hyperthermia). However, selective b1-adrenergic antagonists (such as metoprolol or atenolol) are not as effective in relieving the autonomic response. Clonidine (alpha 2 adrenergic agonist), on the other hand, not only controls hypertension, but also has a sedative and stabilizing effect on behavior by interrupting feedback to the system. There is no consensus on the isolated or associated use of these medications. (2, 5, 7, 8). In our case, we opted for double treatment with propranolol and clonidine, after evaluation together with a cardiology service. Baclofen is a gamma-aminobutyric acid receptor agonist. Helps with spasticity, stiffness and pain in patients with PEH, avoiding contractures. In cases where dysautonomia or posturing persists, the use of intrathecal infusion of baclofen (ITB) has been reported (5, 8). Gabapentin, an analog of GABA, was originally developed as an anticonvulsant. However, it may be more useful in the management of painful neuropathies, spasticity, and tremor; which may also be related to its slightly sedative properties. Because of a similar mechanism of action, it is considered an alternative to oral baclofen (5, 8)

However, as observed in our case, the patient did not respond to the usual treatment of PSH, requiring alternative treatments such as trihexyphenidyl and biperiden. Trihexyphenidyl is a selective muscarinic acetylcholine receptor antagonist, blocking cholinergic activity centrally and peripherally. It is also thought to increase the availability of dopamine. The mechanism of action of trihexyphenidyl in reducing dystonia is believed to be in the basal ganglia where it reduces acetylcholine and increases dopamine. By treating dystonia and its associated impairments, hope to improve activity and decrease associated pain and discomfort (11). Already the biperiden is an anticholinergic drug used in treatment of Parkinson disease and neuroleptic-induced extrapyramidal motor side effects (12). Some studies demonstrate high dose anticholinergic therapy is beneficial in patients with dystonia, independent of whether dystonia is generalized or segmental, sporadic or familial, adult or juvenile onset (13). Our choice of biperiden is based on our familiarity with it.

In refractory cases, due to the risk of potential non-reversible injury to the CNS and cardiac damage, one can opt for the continuous use of benzodiazepines, propofol, opioids or dexmedetomidine (4, 7, 8).

CONCLUSION

Our patient meets the criteria as recommended by Baguley et al. for the diagnosis of PSH, in addition to the diagnosis being favored by the good response to the treatment instituted. In this case, one of the factors that delayed the diagnosis and earlier management of the patient, were the episodes of sepsis, which were believed to be influencing the persistent fever and motor worsening.

There are no guidelines available for an appropriate regimen and most of the patients require multiple medications from different classes for symptom control. We obtained improvement in dystonic movements with a medication little reported in PSH studies, but which, as observed, is a possibility to be considered.

Finally, further studies are needed to evaluate therapies to be carried out individually or in sequence (in an escalation pattern), in addition to a more complete analysis of the pathophysiology of the disease.

ETHICS AND CONSENT

Patient has consented with the publication of the manuscript. The authors confirm that the approval of an institutional review board was not required for this work because patient have formally consented with the publication of the case report.

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