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CASE REPORT

Dexmedetomidine for Paroxysmal Sympathetic Hyperactivity in a Patient with Traumatic Brain Injury: A Case Report in the Intensive Care Unit

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ABBREVIATIONS:
ICU: Intensive Care Unit
TBI: Traumatic Brain Injury
GCS: Glasgow coma scale
CT: Computerized tomography
ICP: Intracranial Pressure
WCC: White Cell Count
CSF: Cerebrospinal Fluid
PSH: Paroxysmal Sympathetic Hyperactivity

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ABSTRACT

In this case report we describe the course of a patient with severe traumatic brain injury who, upon withdrawal of sedation, presented the characteristic clinical signs of paroxysmal sympathetic hyperactivity and responded to the combination of dexmedetomidine infusion and oral metoprolol. We present the diagnostic and therapeutic rationale that guided our decisions and summarize the current knowledge on the topic.

INTRODUCTION

Paroxysmal sympathetic hyperactivity presents a diagnostic and therapeutic challenge in intensive care medicine. If undiagnosed, it can delay successful weaning from sedation and mechanical ventilation and become a real threat to patients' life and neurological outcome due to hyperthermia or hemodynamic derangement. To our knowledge there are four cases in the medical literature describing the use of dexmedetomidine for paroxysmal sympathetic hyperactivity and only one of them discusses a patient with head trauma.

CASE PRESENTATION

A 22 year old male was admitted in the intensive care unit (ICU) following severe traumatic brain injury (TBI), due to a motorcycle road traffic accident, with Glasgow coma scale score (GCS) 4 (eye opening=1, motor=2, verbal=1). Computerized tomography (CT) of the brain is shown in Figure 1. Neurosurgical consultation advised conservative management. The patient's course was complicated by intracranial pressure (ICP) spikes as high as 45 mmHg and an ICP protocol was applied, including hyperosmolar therapy and maintenance of normothermia. A barbiturate infusion was added on day eight post admission for five days and was discontinued following

Conflict of Interest: none declared

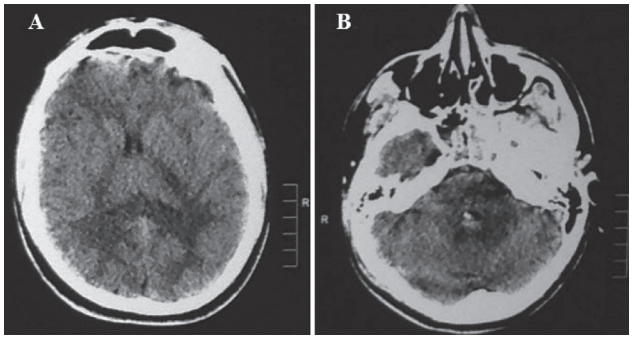

FIGURE 1. Computerized tomography of the brain on admission shows cerebral contusions, traumatic subarachnoid hemorrhage, pneumocephalus and significant brain edema (loss of grey-white matter differentiation, reduced size of ventricles and subarachnoid space). There are also fractures of the sphenoid sinus, of the left orbit and temporal bone.

adequate ICP control. Paracetamol and intravenous antibiotics (meropenem and colistin) were also administered to treat febrile episodes but an infection source was not identified.

Two days after the discontinuation of barbiturates the patient opened his eyes spontaneously. He was febrile 38.6 °C on paracetamol 3 g/day, tachycardic (120-140 bpm), tachypneic (35-38 breaths/min, arterial CO_2=30-32 mmHg) and hypertensive (systolic blood pressure 150-180 mmHg). Diaphoresis, dilated pupils reacting briskly to light and extensor posturing were also noticed. Posturing, tachycardia and hypertension were elicited with tactile stimuli and suction of the endotracheal tube. Repeated brain CT scan showed improvement of edema and the presence of sphenoid sinus fluid collections. His chest X-ray was normal. Inflammatory markers were as follows: white cell count (WCC) = 11 x 10^3/μL 80% neutrophils, C-reactive protein (CRP) = 9.01 mg/dL and procalcitonin (PCT) = 0.07 ng/mL. A lumbar puncture and Cerebrospinal fluid (CSF) analysis showed 10 cells/mm^3 (7 lymphocytes, 3 neutrophils), 450 red blood cells/mm^3 (80% "recent"), glucose 60 mg/dL (serum glucose 100 mg/dL) and total protein 62 mg/dL. The patient was sedated with propofol and remifentanyl. Tracheostomy and endoscopic drainage of the sphenoid sinus were performed on day 17. *Pseudomonas aeruginosa* and *Acinetobacter baumanii* sensitive to meropenem and colistin were cultured from bronchial secretions and sphenoid sinus samples respectively. Thyroid stimulating hormone was normal.

Sedation was discontinued after the tracheostomy and the patient was successfully weaned from mechanical ventilation. Episodes (two to three times a day) of hypertension, tachypnea, tachycardia, pupil dilation and posturing emerged on minimal stimulation and were not alleviated with morphine 1mg/h and esmolol 50 μg/Kg/min. Diazepam 10 mg iv was also ineffective. Dexmedetomidine infusion was initiated at this phase at 0.024 μg/Kg/min. Morphine, esmolol and diazepam were gradually withdrawn and an electroencephalogram was performed that showed no evidence of epilepsy.

Oral metoprolol 25 mg twice daily was added in an attempt to wean off dexmedetomidine within 72 hours. This was not successful due to symptom relapse and dexmedetomidine was continued and titrated to symptom control (Fig. 2). As metoprolol dose was gradually increased and the episodes of posturing, hypertension tachycardia and diaphoresis became sparser (<2 per day) dexmedetomidine infusion rate was reduced and was finally discontinued 12 days after its initiation. The patient was discharged from ICU afebrile on metoprolol 75 mg twice daily with improved neurological status. After closure of his tracheostomy he was able to go home with a physiotherapy plan, fully oriented and obeying commands.

DISCUSSION

Episodic agitation, diaphoresis, hyperthermia, tachycardia, tachypnea and rigid decerebrate posturing after severe brain injury were first described by Strich in 1956 using the term "brainstem attacks".[1] The term Paroxysmal sympathetic hyperactivity (PSH) has been suggested as a clinically more accurate term for the condition.[2] Diagnostic criteria proposed for this entity are: i) history of severe brain injury (Rancho Los Amigos level IV), ii) core temperature of at least 38.5 °C, iii) pulse rate of at least 130 bpm, iv) respiratory rate of at least 30 breaths/min, v) agitation, vi) diaphoresis, and vii) dystonia (i.e. rigidity or decerebrate posturing).[3] The frequency and duration of the symptoms must be at least 1 cycle per day for 3 days. Aortic trauma and medical conditions shown in Table 1 must be ruled out.[4] The pathophysiology of PSH remains unclear but current literature supports dysfunction of autonomic

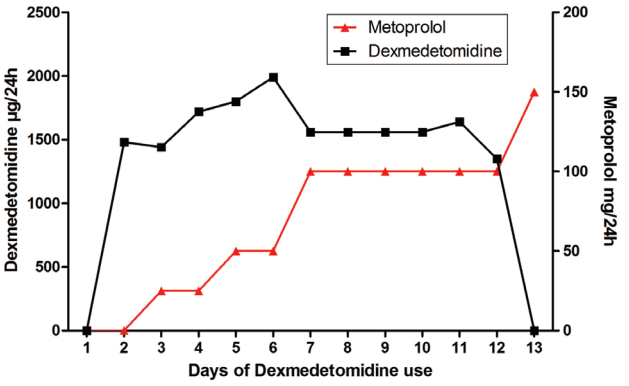

FIGURE 2. Daily dosage requirements of dexmedetomidine and metoprolol. Filled triangle: total daily dose of dexmedetomine. Filled square: total daily dose of metoprolol. Hourly infusion range for dexmedetomidine was 0.005-0.025 μg/Kg/min. Dose reductions were attempted on day 3 and daily afterwards.

TABLE 1. Key findings for differential diagnosis between Paroxysmal Sympathetic Hyperactivity syndrome and other conditions

Diagnosis	Findings that may differentiate from PSH
Malignant hyperthermia	History of anesthetic agent exposure, rhabdomyolysis (high CK) and myoglobinuria are present
Neuroleptic malignant syndrome (NMS)	History of neuroleptic medication use (1-4 weeks prior to presentation), blood pressure may be low, rhabdomyolysis (CK) and myoglobinuria are present
Lethal catatonia	Subacute onset of insomnia, anorexia, delusions. Occurring in patients without prior exposure to predisposing medications (unlike NMS). Psychomotor retardation usually present. CK may be high
Increased ICP	Heart and breathing rate may be low and irregular, ICP monitoring and/or brain imaging are usually diagnostic
Central fever	Fever may be the only sign present. Blood pressure heart rate and pupil size are usually unaffected. Rigidity is usually absent
Infections/Sepsis	Hypertension, diaphoresis, rigidity and pupillary dilation are usually absent. WBC, CRP, lactic acid elevated. Positive cultures. Imaging suggestive
Systemic Inflammatory Response Syndrome (SIRS)	Hypertension is usually absent. Presentation is not episodic. Rigidity/decerebrate posturing are absent
Non convulsive epilepsy	EEG findings can be diagnostic. Elevated post-ictal prolactin is suggestive
Agitation	The patient exhibits purposeful movement, pyrexia is absent
Narcotic withdrawal	Dystonia, extension posturing and pyrexia are absent
Autonomic dysreflexia	History of spinal cord lesion, pupil dilation is absent
Pulmonary embolism	Oxygenation defect, CTPA may be diagnostic. Rigidity/decerebrate posturing are absent
Thyroid storm	Exophthalmos, cardiac arrhythmias and GI symptoms. Deregulation of thyroid hormones is present
Serotonin syndrome	History of serotonergic medication use. Diarrhea, hypomania/confusion, ataxia usually present
Delirium tremens	History of alcohol abuse associated with alcohol withdrawal. Palpitations, fatigue, nausea and vomiting, changes in mental status and hallucinations

PSH: paroxysmal autonomic hyperactivity, ICP: IntraCranial Pressure, WBC: white blood cells, CRP:C-reactive protein, EEG: electroencephalograph, CK: Creatinine Kinase, CTPA: computed tomography pulmonary angiogram, GI: gastrointestinal, SSRI: selective serotonin reuptake inhibitor

centers in the diencephalon (thalamus or hypothalamus) or their connections to cortical, subcortical, and brainstem loci that mediate autonomic function.[5-7]

Our patient fulfilled the criteria for PSH. CSF examination was consistent with traumatic subarachnoid hemorrhage and did not support a diagnosis of meningitis. Sphenoiditis related to craniofacial fractures could be the cause of hyperventilation, pyrexia and tachycardia, but cannot explain the hypertension, the decerebrate posturing and the episodic presentation of symptoms. Opiate withdrawal, pain and agitation would likely respond to intravenous morphine. We therefore attribute the clinical signs to PSH possibly overlapping with infection.

Adequate control of PSH is important in order to avoid complications such as intracranial or severe arterial hypertension, cardiac arrhythmias, dehydration and secondary brain injury caused by hyperthermia. Patients should receive sufficient hydration and hyperthermia must be treated aggressively. Pain, bladder distention and body turning that can trigger the symptoms should be avoided.[8] Table 2 presents the pharmacologic treatment options for PSH and for conditions that may be ovarlapping with or mimicking it.[9-12] Our patient did not respond to morphine, β blocker and diazepam. We decided to try dexmedetomidine in combination with a β blocker at that stage. Dexmedetomidine is a selective α_2 receptor agonist whose sedative effects are mediated through decreased firing of locus ceruleus in the brainstem.[13-15] The α_2 agonists' pattern of sedation is quite different from that of other sedative agents: patients can be aroused, their neu-

TABLE 2. Pharmacological management of PSH and clinically overlapping syndromes

	Opiates	β-blockers	Bromocryptine	Clonidine	Dexmedetomidine	Baclofen (intrathecal)	Benzodiazepines	Anticonvulsants	Dantrolene
PSH	✓	✓	✓	✓	✓	✓	✓	✓	✓
Malignant hyperthermia	✓	✓					✓		✓
Neuroleptic malignant syndrome			✓	✓			✓	✓	✓
Lethal catatonia							✓	✓	
Increased ICP	✓						✓	✓	
Central fever				✓		✓			✓
Non convulsive epilepsy	✗		✗				✓	✓	
Agitation	✓				✓		✓		
Opiate withdrawal	✓			✓			✓	✓	
Delirium tremens	✓	✓		✓	✓		✓	✓	
Autonomic dysreflexia	✓			✓		✓	✓	✓	✓
Thyroid storm		✓					✓		
Post anesthetic shivering	✓			✓	✓		✓		

PSH: Paroxysmal Sympathetic Hyperactivity, ICP: Intracranial Pressure, SIRS: Systemic Inflammatory Response Syndrome. ✓: treatment is indicated, ✗: treatment is contraindicated. See references.[7,19]

rological performance is usually well preserved[16,17] and the respiratory system is not depressed.[18,19] Main adverse effects are hypotension and bradycardia.

We preferred dexmedetomidine to clonidine, an older α_2 receptor agonist, for our patient because it binds α_2 receptors eight times more avidly than clonidine and is shorter acting making dose titration easier.[20] Figure 2 shows the doses of the two medications used. In the cases where dexmedetomidine use in PSH has been described, continuous infusions were administered for up to 72 hours.[21,22] Our patient required a longer infusion for symptom control following the gradual titration of metoprolol to 75 mg twice a day.

In conclusion, our case shows that dexmedetomidine can be used in "difficult to wean" post TBI patients that present symptoms of PSH. Since PSH shares common features with other conditions commonly encountered in the ICU the possibility of another diagnosis mimicking or overlapping with PSH must be taken into account when making therapeutic choices. Evidence on the effectiveness of treatment comes only from case reports and case series and should be the target of research in intensive care and neurorehabilitation.

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