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

Ismini Lasithiotaki,1 Aikaterini Megalou,1 Stefanos Korfias,2 Stamatis Banos,2 Charikleia S. Vrettou1

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...
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.

Figure 2. Daily dosage requirements of dexmedetomidine and metoprolol. Filled triangle: total daily dose of dexmedetomidine. 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.

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 nervous system.

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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 overlapping 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 α2 receptor agonist whose sedative effects are mediated through decreased firing of locus ceruleus in the brainstem.13-15 The α2 agonists’ pattern of sedation is quite different from that of other sedative agents: patients can be aroused, their neu-

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

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Findings that may differentiate from PSH</th>
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<tbody>
<tr>
<td>Malignant hyperthermia</td>
<td>History of anesthetic agent exposure, rhabdomyolysis (high CK) and myoglobinuria are present</td>
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<tr>
<td>Neuroleptic malignant syndrome (NMS)</td>
<td>History of neuroleptic medication use (1-4 weeks prior to presentation), blood pressure may be low, rhabdomyolysis (CK) and myoglobinuria are present</td>
</tr>
<tr>
<td>Lethal catatonia</td>
<td>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</td>
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<tr>
<td>Increased ICP</td>
<td>Heart and breathing rate may be low and irregular, ICP monitoring and/or brain imaging are usually diagnostic</td>
</tr>
<tr>
<td>Central fever</td>
<td>Fever may be the only sign present. Blood pressure heart rate and pupil size are usually unaffected. Rigidity is usually absent</td>
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<tr>
<td>Infections/Sepsis</td>
<td>Hypertension, diaphoresis, rigidity and pupillary dilation are usually absent. WBC, CRP, lactic acid elevated. Positive cultures. Imaging suggestive</td>
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<tr>
<td>Systemic Inflammatory Response Syndrome (SIRS)</td>
<td>Hypertension is usually absent. Presentation is not episodic. Rigidity/decerebrate posturing are absent</td>
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<td>Non convulsive epilepsy</td>
<td>EEG findings can be diagnostic. Elevated post-ictal prolactin is suggestive</td>
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<tr>
<td>Agitation</td>
<td>The patient exhibits purposeful movement, pyrexia is absent</td>
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<tr>
<td>Narco tic withdrawal</td>
<td>Dystonia, extension posturing and pyrexia are absent</td>
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<tr>
<td>Autonomic dysreflexia</td>
<td>History of spinal cord lesion, pupil dilation is absent</td>
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<tr>
<td>Pulmonary embolism</td>
<td>Oxygenation defect, CTPA may be diagnostic. Rigidity/decerebrate posturing are absent</td>
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<tr>
<td>Thyroid storm</td>
<td>Exophthalmos, cardiac arrhythmias and GI symptoms. Deregulation of thyroid hormones is present</td>
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<tr>
<td>Serotonin syndrome</td>
<td>History of serotonergic medication use. Diarrhea, hypomania/confusion, ataxia usually present</td>
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<tr>
<td>Delirium tremens</td>
<td>History of alcohol abuse associated with alcohol withdrawal. Palpitations, fatigue, nausea and vomiting, changes in mental status and hallucinations</td>
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</tbody>
</table>

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
DEXMEDITOMIDINE FOR PSH IN A PATIENT WITH TBI

Table 2. Pharmacological management of PSH and clinically overlapping syndromes

<table>
<thead>
<tr>
<th></th>
<th>Opiates</th>
<th>β-blockers</th>
<th>Bromocriptine</th>
<th>Clonidine</th>
<th>Dexmedetomidine</th>
<th>Buprenorphine (intrathecal)</th>
<th>Benzodiazepines</th>
<th>Anticonvulsants</th>
<th>Dantrolene</th>
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<tbody>
<tr>
<td>PSH</td>
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<td>Malignant hyperthermia</td>
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<td>Increased ICP</td>
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<td>Central fever</td>
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<td>Agitation</td>
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<td>Opiate withdrawal</td>
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<td>Delirium tremens</td>
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<td>Thyroid storm</td>
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<td>Post anesthetic shivering</td>
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PSH: Paroxysmal Sympathetic Hyperactivity, ICP: Intracranial Pressure, SIRS: Systemic Inflammatory Response Syndrome. ✔: treatment is indicated, ✗: treatment is contraindicated. See references.28

rological performance is usually well preserved\textsuperscript{16,17} and the respiratory system is not depressed.\textsuperscript{16,19} Main adverse effects are hypotension and bradycardia.

We preferred dexmedetomidine to clonidine, an older α\textsubscript{2} receptor agonist, for our patient because it binds α\textsubscript{2} receptors eight times more avidly than clonidine and is shorter acting making dose titration easier.\textsuperscript{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.\textsuperscript{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.

REFERENCES

5. Nosaka S. Hypertension induced by extensive medial antero-
median hypothalamic destruction in the rat. *Jpn Circ J* 1966;
30:509-523.

6. Reis DJ GP, Nathan MA. Hypertension, adrenal catecholamine
release, pulmonary edema, and behavioral excitement elicited
from the anterior hypothalamus in rat. Usdin E KR, Kopin I, eds.

1985.

8. Rabinstein AA. Paroxysmal sympathetic hyperactivity in the

9. Scutariu MKC, Oslobanu A, Florian Şt I. Paroxysmal autonomic
instability with dystonia after severe traumatic brain injury – a

10. Safadieh L, Sharara-Chami R, Dabbagh O. Paroxysmal au-
tonomic instability with dystonia after pneumococcal menin-

11. May CC, Oyler DR, Parli SE, Talley CL. Rectal propranolol
controls paroxysmal sympathetic hyperactivity: a case report.

12. Letzkus L, Keim-Malpass J, Kennedy C. Paroxysmal sym-
pathetic hyperactivity: Autonomic instability and muscle
over-activity following severe brain injury. *Brain Inf* 2016;
30:1181-1185.

lines for the management of pain, agitation, and delirium in
adult patients in the intensive care unit. *Crit Care Med* 2013;
41:263-306.

14. Patel SB, Kress JP. Sedation and analgesia in the mechanically
ventilated patient. *Am J Respir Crit Care Med* 2012; 185:486-
497.

15. Bhana N, Goa KL, McClellan KJ. Dexmedetomidine. *Drugs*

16. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intra-
venous dexmedetomidine in humans. I. Sedation, ventilation,

17. Triltsch AE, Welte M, von Homeyer P, et al. Bispectral index-
guided sedation with dexmedetomidine in intensive care: a
prospective, randomized, double blind, placebo-controlled

18. Hoy SM, Keating GM. Dexmedetomidine: a review of its use
for sedation in mechanically ventilated patients in an intensive
care setting and for procedural sedation. *Drugs* 2011; 71:1481-
1501.

19. Venn RM, Hell J, Grounds RM. Respiratory effects of dex-
medetomidine in the surgical patient requiring intensive care.

Care* 2001; 7:221-226.

for the treatment of paroxysmal autonomic instability with

22. Kern J, Bodek D, Niazi OT, Maher J. Refractory case of
paroxysmal autonomic instability with dystonia syndrome