Case Report

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Efficacy of trazodone for treating paroxysmal sympathetic hyperactivity presenting after thalamic hemorrhage: A case report

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Summary **Paroxysmal sympathetic hyperactivity (PSH) is a clinical condition characterized by abnormal paroxysmal surges in sympathetic nervous system activity. PSH is known to occur after severe head injury and hypoxic encephalopathy. Cases of PSH that develop after stroke have been reported worldwide; however, PSH is not commonly reported in the field of stroke research in Japan. Some studies have suggested that gabapentin may improve the symptoms of PSH. To our knowledge, this is the first case report demonstrating the efficacy of trazodone for the treatment of PSH that developed after thalamic hemorrhage. A 45-year-old woman presented to our clinic with headache and paralysis of the left side of her body after experiencing right thalamic hemorrhage; a conservative treatment was initiated at our hospital. Immediately upon hospitalization, she developed high fever, tachycardia, tachypnea, constipation, and overactive bladder and had breathing difficulties. Blood sampling revealed elevated levels of myocardial escape enzymes; however, coronary angiography did not show any significant stenosis or occlusion. The patient's symptoms improved after the administration of trazodone. She was diagnosed with catecholamine cardiomyopathy associated with PSH after intracranial hemorrhage and was subsequently transferred to a recovery and rehabilitation hospital unit where the oral administration of trazodone continued. Prolonged PSH contributes significantly to the impairment of daily activities in patients with stroke; therefore, early diagnosis and treatment are critical. Here, we report on the efficacy of trazodone as an effective treatment option for improving clinical outcomes and reducing the stay in the stroke care unit.**

Keywords: Paroxysmal sympathetic hyperactivity, thalamic hemorrhage, trazodone

1. Introduction

Paroxysmal sympathetic hyperactivity (PSH) is a clinical condition characterized by abnormal paroxysmal surges in sympathetic nervous system activity. Although the symptoms of PSH have been identified for longer than 60 years, it has had over 31 different names, including dysautonomia, paroxysmal autonomic instability with dystonia, paroxysmal sympathetic storm, sympathetic storm, autonomic storm, diencephalic seizure, and autonomic dysfunction syndrome, to name a few, which makes it very difficult to identify (*1,2*). PSH often occurs after severe head injury and hypoxic encephalopathy, although it is also known to develop after stroke. However, in Japan, limited evidence regarding a connection between PSH and stroke exists (*3,4*). Therapeutic drugs, including morphine, benzodiazepines, beta-blockers, baclofen, gabapentin, and clonidine, are commonly used to suppress PSH. The inadequate therapeutic effect of these drugs necessitates the inclusion of bromocriptine (a dopamine agonist) to the treatment regimen (*5-8*). However, evidence suggests that such treatment regimens are therapeutically

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ineffective (*7*). Moreover, antiepileptic drugs are generally ineffective for treating PSH. Alternatively, multiple papers have reported on the efficacy of gabapentin for treating PSH (*1-3,5,9,10-13*), which is considered to improve the symptoms by controlling the suppressive nerve stimulation (*5*). However, there is no report on the therapeutic effect of sympathetic blockers, *i.e.*, α blockers. To our knowledge, the efficacy of trazodone for treating PSH that developed after thalamic hemorrhage has not been reported. Here, we describe the case of a patient who developed PSH after right thalamic hemorrhage, which was successfully treated with trazodone.

2. Case Report

A 45-year-old woman presented to our clinic with headache and left paralysis after a right thalamic hemorrhage. She had a medical history of hypertension but did not use any antihypertensive medication. Neurological assessments revealed paralysis and sensory disturbances in her left upper and lower limbs and left central facial paralysis. She scored 8/42 on the National Institutes of Health Stroke Scale; her modified Rankin scale score at admission was 3, and her blood pressure at hospitalization was 258/143 mmHg, indicative of a hypertensive emergency. Electrocardiography and blood analyses, including blood cell counts, biochemistry, and coagulation parameters, revealed no abnormalities. A plain head computed tomography showed right thalamic hemorrhage (Figure 1A), and susceptibility-weighted magnetic resonance imaging showed cerebral microbleeds in the contralateral basal ganglia without any blood vessel malformations (Figure 1B). Magnetic resonance angiography revealed no aneurysms or blood vessel malformations (Figure 1C), and a chest radiograph showed no apparent heart expansion or pulmonary edema (Figure 1D).

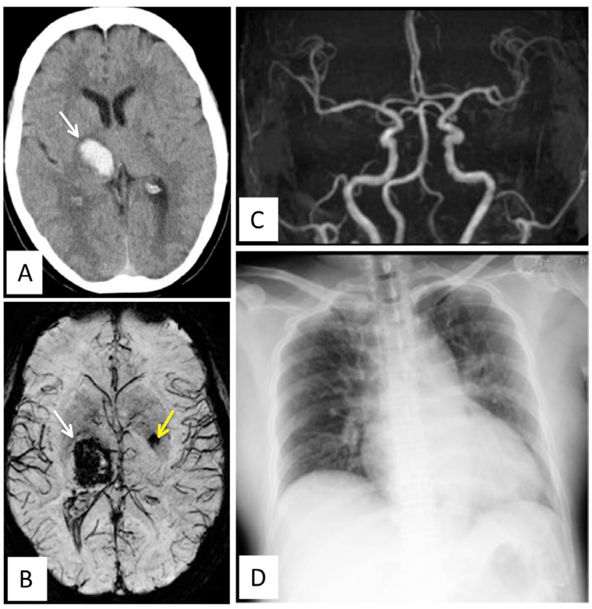

Figure 1. Clinical imaging for stroke signs upon initial presentation. (A) Head plane computed tomography image reveals a right thalamic hemorrhage (white arrowhead). **(B)** Susceptibility-weighted magnetic resonance image shows cerebral microbleeds (yellow arrowhead) in the left basal ganglia but no blood vessel malformations (white arrowhead). **(C)** Magnetic resonance angiography image reveals no aneurysms or blood vessel malformations. **(D)** Chest radiography shows no apparent heart expansion or pulmonary edema.

The patient was administered nicardipine as a conservative treatment for management of her blood pressure; the targeted systolic blood pressure was ≤ 140 mmHg. Immediately upon hospitalization, the patient developed a sudden high fever, accompanied by mass sweating, tachycardia, a significant increase in blood pressure, tachypnea, constipation, overactive bladder, and breathing difficulties. Head computed tomography images showed no enlargement of the hematoma on day 1 of hospitalization, and she was prescribed azilsartan (40 mg/day), amlodipine (10 mg/day), and trichlormethiazide (2 mg/day) to manage the hypertension.

On day 3 of hospitalization, the patient did not report chest pain but had difficulty breathing and insomnia. Blood sampling revealed elevated levels of myocardial escape enzymes, including troponin T, 0.34 ng/mL; creatine kinase, 446 U/L; lactate dehydrogenase, 292 U/L; adrenaline, 68 pg/mL; noradrenalin, 851 pg/mL; dopamine, 25 pg/mL; renin activity, 3.0 ng/mL/h; aldosterone, 183 pg/mL; and cortisol, 21.6 µg/dL. All cardiac parameters were above the normal levels, except adrenaline. No abnormalities were observed on electroencephalography; however, it showed ST-segment and T-wave changes in leads I, II, aVL, V5, and V6 (Figure 2A). Cardiac ultrasonography, performed on day 3 of hospitalization,

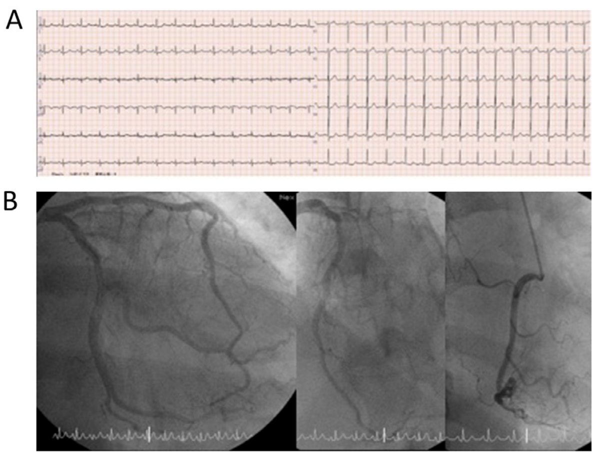

Figure 2. Examinations performed on days 5 and 9 of hospitalization. (A) Electrocardiography performed on day 5 shows ST-segment and T-wave (ST-T) changes in leads I, II, aVL, V5, and V6. **(B)** Coronary angiography images acquired on day 9 do not show any significant coronary artery stenosis or occlusion.

showed no wall motion abnormalities. Based on the series of systemic symptoms experienced, including the autonomic symptoms that were indicative of an intracranial hemorrhage associated with PSH, she was administered trazodone (50 mg/day), beginning on day 5 of hospitalization. As we had experienced a case in which trazodone was effective as a sympathetic blocker for Barré-Lièou syndrome (BLS), based on the post-traumatic sympathetic hyperactivity theory, we hoped that it would also be effective for PSH, which is a similar pathological condition.

Under this treatment regimen, the patient's breathing difficulties were rapidly alleviated and most of the other autonomic symptoms also improved. However, the periodic fever was sustained and was treated with an antipyretic, and she continued her rehabilitation without additional problems. Coronary angiography performed on day 9 of hospitalization showed no significant coronary artery stenosis or occlusion (Figure 2B), allowing the exclusion of acute coronary syndrome from the diagnosis. Because the patient's symptoms improved significantly after the administration of trazodone, she was diagnosed with catecholamine cardiomyopathy associated with PSH.

By day 10 of hospitalization, her general condition had stabilized, and she was moved from the stroke care unit to the general ward. She was transferred to a separate recovery rehabilitation hospital 20 days after admission, where the trazodone treatment (50 mg/day) continued. Trazodone was gradually reduced and eventually stopped 1 month after initial admission. No relapse of PSH was observed until 6 months after admission, and the dose of azilsartan was gradually decreased to 20 mg/day, and the patient had a modified Rankin scale score of 2 at the outpatient follow-up examination 10 months after admission. Written informed consent was obtained from the patient for publication of this case report and the accompanying images, and the study design was approved by the appropriate ethics review board.

3. Discussion

To our knowledge, the present report is the first to demonstrate the efficacy of trazodone for the treatment of PSH that developed after thalamic hemorrhage. PSH has only recently been defined (*1*), and is characterized by excessive autonomic symptoms, including high fever, high blood pressure, tachycardia, tachypnea, perspiration, and muscle tone abnormality. PSH occurs after severe brain injury, usually during a state of paroxysmal sympathetic excitement (*10*). Following paroxysmal excitement, the autonomic symptoms typically occur approximately five times a day, each episode lasting approximately 30 min. PSH causes hyperthermia, dehydration, muscle mass reduction, and muscle contracture and has a serious effect on reversion, such as symptom recurrence or prolonged requirement of intensive care unit management, or causes serious secondary sequelae (*5,11-13*). Although these complications can be avoided by early diagnosis and treatment (*6-8,14,15*), the detection of PSH is impossible without any knowledge of the underlying pathophysiology. Previously, the lack of a clear definition and diagnostic criteria resulted in poor understanding of the condition, and moreover, the variations in the symptoms complicated the diagnosis of PSH. In our case, we did not observe an epileptic wave on electroencephalography and antiepileptic drugs were not administered; therefore, a diagnosis of epilepsy was rejected. Since the series of her general symptoms resembled post-traumatic sympathetic hyperactivity to the prevailing BLS (*16*), we suspected PSH, and the diagnosis was confirmed once the symptoms met the known diagnostic criteria (*1*). We previously reported on the efficacy of trazodone for BLS (unpublished observations), and as PSH, similar to BLS, is a sympathetic condition, we assumed that trazodone use would be effective in this case.

Currently, there are two theories (*11,15*) that explain the pathophysiology of PSH. Specifically, it is theorized that the decoupling of the sympathetic excitement center of the hypothalamus and brainstem from the control of higher functioning brain regions, such as the cerebral cortex, results in a state of sympathetic excitement. The second theory suggests that when the midbrain or brainstem, regions that control afferent stimulation in the spinal cord, is injured, it becomes impossible to suppress the stimulation, which leads to hyperexcitability in the afferent pathway of the spinal cord. Currently, the latter theory has greater support (*11,15*).

Research has shown that PSH most commonly occurs in younger individuals; indeed, Hughes *et al*. (*15*) reported that the mean age of patients with PSH was 33.6 years, which is consistent with the age of our patient. Few reports of stroke-associated PSH in Japan have been published (*1,16*). Although the reason for this is unknown, awareness and understanding of the pathological condition are poor; therefore, it is possible that the occurrence of this condition has not been accurately reported.

The patient was diagnosed with PSH associated with intracranial hemorrhage. Interestingly, she often complained of respiratory distress. After assessing the coronary angiography, cardiac ultrasonography examination, blood sampling, and electrocardiography results, the patient was also diagnosed with catecholamine cardiomyopathy caused by PSH. To our knowledge, this is the first reported case of stroke-related PSH with catecholamine cardiomyopathy.

Trazodone, a well-known antidepressant drug widely used worldwide, works as a 5-hydroxytryptamine (5-HT2) and α1-adrenergic receptor antagonist and a serotonin reuptake inhibitor (*17*). Symptoms improved after trazodone administration to patients with BLS and PSH, which are considered similar pathological conditions involving sympathetic hyperactivity, and we assume that trazodone's alpha blocking action was responsible for this effect. It was considered that this action could suppress sympathetic hyperactivity. There have been few reports of trazodone side effects, such as 270 cases of drowsiness (3.64%), 215 cases of dry mouth (2.90%), and 134 cases of constipation (1.81%) (*18*) and it is relatively safer for use in the elderly. In our case, trazodone, which is often used for treating depression because of its mechanism related to alpha-adrenoceptor inhibition (*17*), was effective for treating PSH.

Recognition of PSH is crucial for the rapid recovery of patients with traumatic brain injury or stroke, even when they are still in intensive care units. It is also important to reduce complication rates and the length of hospitalization (*6*). PSH is a common syndrome, and failure to recognize this condition is associated with increased morbidity and mortality, higher health costs, longer hospitalization, and poorer outcomes (*3*). In the present case, we believe that the early diagnosis and treatment of PSH, considering the symptoms of paroxysmal sympathetic hyperactivity that occurred after intracerebral hemorrhage, contributed to the overall short duration of hospitalization (in the stroke care unit and general hospital ward). In the future, it is desirable to accumulate more cases to conclusively comment on the efficacy of trazodone for PSH.

In conclusion, trazodone was effective in treating PSH in our case, and its use may reduce the overall duration of hospitalization and improve clinical outcomes in affected individuals. Trazodone can be an effective drug for PSH treatment, although further evidence accumulation from a larger number of cases is needed.

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References

1. Baguley IJ, Perkes IE, Fernandez-Ortega JF, Rabinstein AA, Dolce G, Hendricks HT. Paroxysmal sympathetic hyperactivity after acquired brain injury: Consensus on conceptual definition, nomenclature, and diagnostic criteria. J Neurotrauma. 2014; 31:1515-1520.
2. Baguley IJ, Nicholls J, Felmingham K, Crooks J, Gurka JA, Wade LD. Dysautonomia after traumatic brain injury: A forgotten syndrome? J Neurol Neurosurg Psychiatry. 1999; 67:39-43.
3. Inoue D, Miki K, Mori M, Yamada T, Kai Y, Natori Y. Two case reports of paroxysmal sympathetic hyperactivity following craniotomy for cerebral hemorrhages. No Shinkei Geka. 2019; 47:79-84.
4. Hughes JD, Rabinstein AA. Early diagnosis of paroxysmal sympathetic hyperactivity in the ICU. Neurocrit Care. 2014; 20:454-459.
5. Perkes I, Baguley IJ, Nott MT, Menon DK. A review of paroxysmal sympathetic hyperactivity after acquired brain injury. Ann Neurol. 2010; 68:126-135.
6. Rabinstein AA, Benarroch EE. Treatment of paroxysmal sympathetic hyperactivity. Curr Treat Options Neurol. 2008; 10:151-157.
7. Heffernan DS, Inaba K, Arbabi S, Cotton BA. Sympathetic hyperactivity after traumatic brain injury and the role of beta-blocker therapy. J Trauma. 2010; 69:1602-1609.
8. Baguley IJ, Heriseanu RE, Gurka JA, Nordenbo A, Cameron ID. Gabapentin in the management of dysautonomia following severe traumatic brain injury: A case series. J Neurol Neurosurg Psychiatry. 2007; 78:539-541.
9. Mathew MJ, Deepika A, Shukla D, Devi BI, Ramesh VJ. Paroxysmal sympathetic hyperactivity in severe traumatic brain injury. Acta Neurochir (Wien). 2016; 158:2047-2052.
10. Baguley IJ. The excitatory:inhibitory ratio model (EIR model): An integrative explanation of acute autonomic overactivity syndromes. Med Hypotheses. 2008; 70:26-35.
11. Fernandez-Ortega JF, Prieto-Palomino MA, Garcia-Caballero M, Galeas-Lopez JL, Quesada-Garcia B, Baguley IJ. Paroxysmal sympathetic hyperactivity after traumatic brain injury: Clinical and prognostic implications. J Neurotrauma. 2012; 29:1364-1370.
12. Dolce G, Quintieri M, Leto E, Milano M, Pileggi A, Lagani V, Pignolo L. Dysautonomia and clinical outcome in vegetative state. J Neurotrauma. 2008; 25:1079-1082.
13. Perkes IE, Menon DK, Nott MT, Baguley IJ. Paroxysmal sympathetic hyperactivity after acquired brain injury: A review of diagnostic criteria. Brain Inj. 2011; 25:925-932.
14. Samuel S, Allison TA, Lee K, Choi HA. Pharmacological management of paroxysmal sympathetic hyperactivity after brain injury. J Neurosci Nurs. 2016; 48:82-89.
15. Meyer KS. Understanding paroxysmal sympathetic hyperactivity after traumatic brain injury. Surg Neurol Int. 2014; 5:S490-S492.
16. Li Y, Peng B. Pathogenesis, diagnosis, and treatment of cervical vertigo. Pain Physician. 2015; 18:E583-E595.
17. De Tejada IS, Ware JC, Blanco R, Pittard JT, Nadig PW, Azadzoi KM, Krane RJ, Goldstein I. Pathophysiology of prolonged penile erection associated with trazodone use. J Urol. 1991; 145:60-64.
18. Yamada H, Kikuchi R, Katayama J, Nakamura A, Miyazaki H. Paroxysmal sympathetic hyperactivity after surgery for cerebral hemorrhagic arteriovenous malformation: A case report. J Stroke Cerebrovasc Dis. 2018; 27:2768-2769.

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