Case Report

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Efficacy of trazodone for treating paroxysmal sympathetic hyperactivity presenting after left temporal subcortical hemorrhage

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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 temporal subcortical hemorrhage. A 49-year-old woman presented to our clinic with mild confusion and sensory aphasia after experiencing left temporal subcortical hemorrhage; a conservative treatment was initiated at our hospital. Immediately upon hospitalization, she developed prolonged consciousness disorder, high fever, tachycardia, malignant hypertension, tachypnea, constipation, and overactive bladder. The patient's symptoms improved after the administration of trazodone. She was diagnosed 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, temporal subcortical 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 (*1-3*). 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 (*3-5*). 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 (*3,6-9*). However, evidence suggests that such treatment regimens are therapeutically ineffective (*8*). Moreover, antiepileptic drugs are generally ineffective for treating PSH. Alternatively, multiple papers have reported on the efficacy of gabapentin for treating PSH (*1,2,4,6, 9,10-14*), which is considered to improve the symptoms by controlling the suppressive nerve stimulation (*6*). However, there is few report on the therapeutic effect of sympathetic blockers, *i.e.*, α blockers (*3*). To our knowledge, the efficacy of trazodone for treating PSH that developed after temporal subcortical hemorrhage has not been reported. Here, we describe the case of a patient who developed PSH after left temporal subcortical hemorrhage, which was successfully treated with trazodone.

2. Case Report

A 49-year-old woman presented to our clinic with mild confusion and sensory aphasia after a left temporal subcortical hemorrhage. She had a medical history

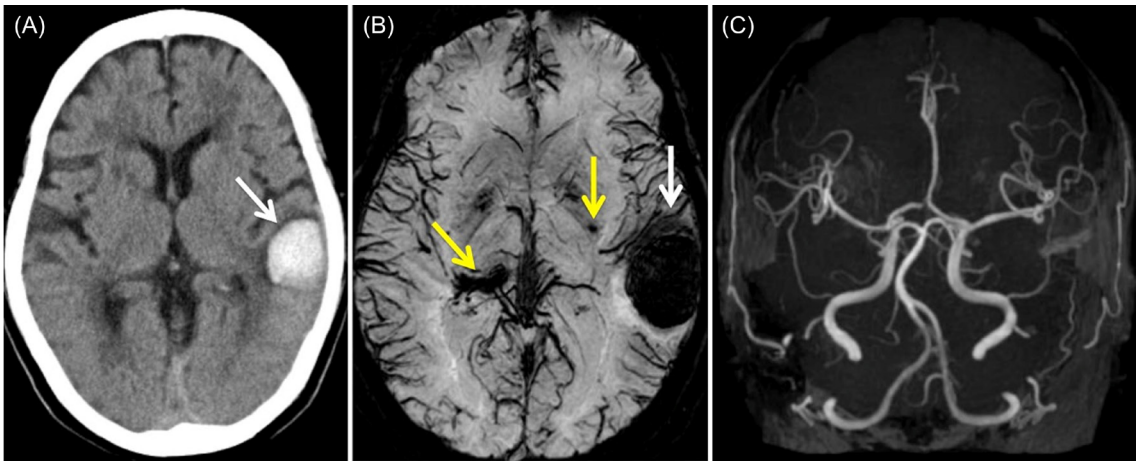

Figure 1. Clinical imaging for stroke signs upon initial presentation. (A) Head plane computed tomography image reveals a left temporal subcortical hemorrhage (white arrowhead). **(B)** Susceptibility-weighted magnetic resonance image shows cerebral microbleeds (yellow arrowhead) in the bilateral basal ganglia but no blood vessel malformations (white arrowhead). **(C)** Magnetic resonance angiography image reveals no aneurysms or blood vessel malformations.

of untreated diabetes only. Neurological assessments revealed no paralysis and sensory disturbances, but mild confusion and sensory aphasia. She scored 5/42 on the National Institutes of Health Stroke Scale; her modified Rankin scale score at admission was 2, and her blood pressure at hospitalization was 201/104 mmHg, indicative of a hypertensive emergency. Electrocardiography revealed sinus tachycardia and blood analyses, including blood cell counts, biochemistry, and coagulation parameters, revealed no aggressive abnormalities requiring treatment. A plain head computed tomography showed left temporal subcortical hemorrhage (Figure 1A), and susceptibility-weighted magnetic resonance imaging showed cerebral microbleeds in the bilateral basal ganglia without any blood vessel malformations (Figure 1B). Magnetic resonance angiography revealed no aneurysms or blood vessel malformations (Figure 1C)).

The patient was administered nicardipine as a conservative treatment for management of her blood pressure; the targeted systolic blood pressure was ≤ 140 mmHg. However, the controls were poor. Immediately upon hospitalization, the patient developed a sudden high fever, accompanied by mass sweating, prolonged consciousness disorder, tachycardia, a significant increase in blood pressure, tachypnea, constipation, overactive bladder. 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), to manage the hypertension.

Electroencephalogram showed no obvious abnormal wave. 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 (100 mg/day), beginning on day 15 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 (*3,15*).

Under this treatment regimen, the patient's tachycardia and malignant hypertension improved promptly, and prolonged consciousness disorder, constipation, overactive bladder, and fever gradually improved. However, aspiration pneumonia was complicated at the time of prolonged consciousness disorder, and antibiotic treatment was required temporarily, Because the patient's symptoms improved significantly after the administration of trazodone, she was diagnosed with PSH after intracranial hemorrhage.

By day 21 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 50 days after admission, where the trazodone treatment (50 mg/day) continued. Trazodone was gradually reduced and eventually stopped 3 month after initial admission. No relapse of PSH was observed until 6 months after admission, 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 temporal subcortical hemorrhage, while there is the reportsof thalamic hemorrhage (*3*). 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 (*11*). 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 (*6,12-14*). Although these complications can be avoided by early diagnosis and treatment (*7-9,16,17*), 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 non-convulsive status epilepticus was negative. Since the series of her general symptoms resembled post-traumatic sympathetic hyperactivity to the prevailing BLS (*15,18*), 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 (*3,15*).

Currently, there are two theories (*12,17*) 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 (*12,17*).

Research has shown that PSH most commonly occurs in younger individuals; indeed, Hughes *et al.* (*17*) 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 (*1,3,18*). 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. 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 (*19*). 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 (*3,15*). 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%) (*20*) 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 (*19*), 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 (*7*). 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 (*4*). 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), while the diagnosis was delayed than the previous report (*3*). 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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