

Effectiveness of Quetiapine for Poststroke Pathological Laughing: Case Report and Review of the Literature

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Abstract: Pathological laughing (PL) is an uncommon distressing symptom that occurs in patients with various neurological disorders. Dysregulation of serotonergic system has been proposed as one of the possible mechanisms resulting in this condition, and selective serotonin reuptake inhibitors have been used for treatment of PL with variable effects. However, the pathogenetic mechanism of PL remains largely elusive, and other treatment choices needs to be explored. This case report illustrates the beneficial effect of quetiapine, an atypical antipsychotic agent with enhancing serotonergic neurotransmitter activity, in a patient with poststroke PL. In addition, previously reported poststroke PL cases searched from PubMed (1993–2010) were also reviewed. In this report, we demonstrate a 42-year-old man who developed PL 4 weeks after a hemorrhage stroke affecting the paramedian pons. He was treated with dextromethorphan initially but did not show obvious response. Then, the medication was shifted to quetiapine at a dosage of 25 mg/d. There was a significant and rapid recovery 2 days after quetiapine treatment. Our observations expand the current knowledge of treatment of PL caused by pontine lesions. Further large-scale controlled trials are warranted to evaluate the beneficial and differential effects of quetiapine on PL.

Key Words: quetiapine, pathological laughing, stroke, pons

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Pathological laughing (PL) is a subset of pathological laughing and crying (PLC), which occurs in patients with various neurological disorders.¹ It is characterized by the presence of inappropriate or easily elicited outbursts of laughter without commensurate feelings.¹ Being distinct from mood disorders such as mania, PL is regarded as a disorder of affect.² The prevalence rate in various neurological disorders varies, and it has been reported in 11% to 34% of patients with stroke.³ The involvement of the descending corticobulbar pathway and pontocerebellar circuits, including the cerebral cortex, the basal ganglia, the cerebral peduncles, the basis pontis, and the cerebellum, has been reported in patients with poststroke PLC.^{1,2,4} The pathogenetic mechanism is proposed to involve partial de-

struction of the serotonergic raphe nuclei or their projections to the hemispheres with resultant dysregulation of serotonergic pathway.¹ In support of this hypothesis, one recent study using single photon emission computed tomography found dysfunction of serotonergic neurotransmission in patients with poststroke PLC.⁵

Given the evidence that dysregulation of serotonergic system is responsible for the PLC, treatment studies have focused on the efficacy of selective serotonin reuptake inhibitors (SSRIs), such as paroxetine, citalopram, fluoxetine, and sertraline, and tricyclic antidepressants (eg, amitriptyline and nortriptyline) for the treatment of PLC.^{6–10} However, the responses to SSRIs are variable, and there are some alternative choices for treatment of patients with PLC, such as lamotrigine, mirtazapine, and venlafaxine.^{11–13} It therefore raises a question that dysfunction of serotonergic system is not the sole neurotransmitter responsible for the development of PLC, and more treatment choices needs to be explored to solve this embarrassing symptom. Herein, we report a patient who experienced delayed-onset PL after pontine hemorrhage and dramatically improved after using quetiapine, an atypical antipsychotic agent. We also systemically reviewed previously reported poststroke PLC cases searched from PubMed (1993–2010).

CASE REPORT

A 42-year-old man was admitted to our hospital for intensive poststroke rehabilitation for his left-side limbs weakness that developed suddenly 3 weeks earlier owing to pontine hemorrhage. He had history of hypertension without any medical control. Noncontrast brain computed tomography soon after his symptoms revealed right-side predominant paramedian pontine hemorrhage (Fig. 1). Routine laboratory examinations did not reveal any significant abnormality. The course of acute care for stroke was smooth except leaving a sequela of left hemiparesis. His consciousness remained clear except mild drowsiness during the first few days. The neurological examination after admission to our hospital revealed left hemiparesis, and he had hyperreflexia with positive Babinski sign on the left side. All sensory modality was intact, and no ataxia was demonstrated. There were mild slurred speech and decreased left nasolabial fold during cranial nerve examinations.

However, 4 weeks after the onset of hemorrhagic stroke, he developed uninhibited laughter over inappropriate context. Casual conversations or ordinary ambiances induced laughter spells, even at bedtime, which leads to sleep disturbance. The laughing spells had been occurring approximately 4 to 6 times per day lasting for 5 minutes per episode. To evaluate the severity, we used the Pathological Laughing and Crying Scale (PLACS), which contains 18 items (9 for pathological laughter and 9 for pathological crying) scored from 0 to 3 points.¹⁴ The PLACS score before any treatment was 19 in the laughter subset and 0 in the crying subset. He denied any previous psychotic

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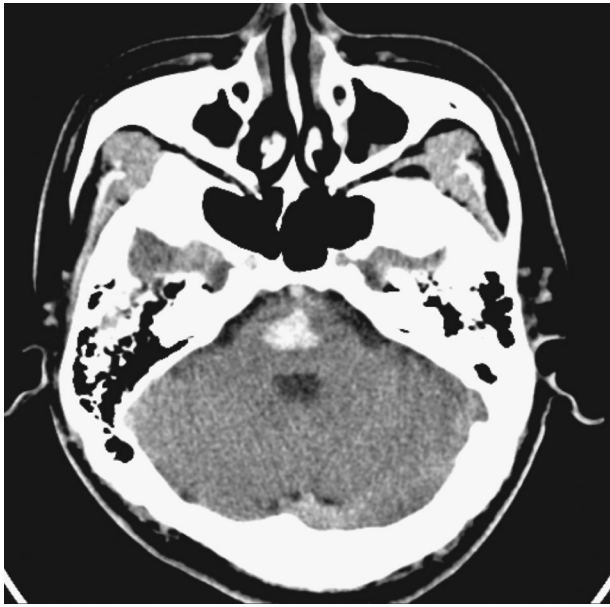


FIGURE 1. Noncontrast head computed tomographic image showing right-side predominant paramedian pontine hemorrhage.

disorder, correlated family history, or recent psychosocial stress. No frontal release sign was detected. Complete neuropsychiatric examination revealed lower-than-average intellectual functions (Wechsler Adult Intelligence Scale, Third Edition) but relatively compatible with his premorbid socioeconomic performance. Otherwise, there were no detected cognitive distortions of mania or depression. The behavior of PL embarrassed him much, which also interfered with the rehabilitation programs. Follow-up brain magnetic resonance imaging (MRI) did not find evidence of a new-onset frontal lobe lesion and only showed subacute pontine hemorrhage. Treatment with diazepam (5 mg/d) was initiated, but symptoms persisted. A regimen of dextromethorphan (120 mg/d), which has been reported to be effective in PL,² was administered 4 days after the onset of PL. Symptoms still persisted and severely bothered his sleep. Therefore, we shifted the medication to quetiapine (25 mg/d) before sleep. Two days later, the frequency of pathological laughter episodes decreased dramatically. The PLACS score decreased to 0 at outpatient follow-up, on day 20 after initiation of quetiapine treatment. The clinical improvement was maintained well under the same dosage of quetiapine in a 3-month follow-up. Furthermore, symptoms of pathological laughter did not recur after decreasing the dosage of quetiapine to 12.5 mg/d (half of the original dosage) in a 4-month follow-up.

DISCUSSION

Our study is the first report to suggest that the atypical antipsychotic agent, quetiapine, could show a benefit for patients with poststroke PL, although the efficacy needs to be confirmed by a further large-scale controlled trial. It is generally accepted that serotonin plays the pivotal role in the development of PLC.^{1,2} The change of serotonergic function in patients with poststroke PLC has also been demonstrated in a controlled study.¹⁵ However, taking into account that the responses to SSRIs for patients with PLC are variable, other neurotransmit-

ters that included dopamine, norepinephrine, and glutamate have been reported to be involved in the pathogenesis of PLC.² In our case, the rapid response (2 days) to quetiapine and the sustained effect without breakthrough of symptoms confirmed its benefit in the treatment of PL.

In addition to the proven efficacy in schizophrenia, quetiapine has been recently approved for the treatment of acute bipolar depression and related mood disorders.^{16,17}

Several pharmacologic mechanisms can be proposed to explain the therapeutic effect of quetiapine in affective symptoms, such as PLC. Quetiapine could act through enhancing central serotonergic neurotransmission via its high affinity for serotonergic receptors, especially for serotonin 2A receptor.¹⁸ Specifically, quetiapine regulates serotonergic system by acting as an antagonist for serotonin 2A receptor and shows partial agonistic activity at serotonin 1A receptor.^{17,18} In keeping with the view that serotonin 2A receptor down-regulation is a critical mechanistic step in increasing synaptic level of serotonin, we believe that quetiapine-associated down-regulation of serotonin 2A receptor may partly contribute to the treatment effect of PLC. In addition, quetiapine also exerts partial agonistic activity at serotonin 1A receptor in the prefrontal cortex, resulting in increasing cortex dopaminergic neurotransmission.¹⁸ Affinity for α 2-adrenoceptor of quetiapine increases extracellular noradrenergic neurotransmitter release in the prefrontal cortex.¹⁹ These combined effects of quetiapine on central serotonergic and monoaminergic systems should be responsible for its beneficial effects on PLC. Our observation implies that there may be other pathways or neurotransmitters being involved in this mysterious syndrome.

Our patient also showed a delayed onset of PL after the hemorrhagic stroke. Emerging evidence has suggested that the onset of PLC is a release phenomenon due to lesions at corticopontomedullary pathway, which dominates the voluntary control of laughing and crying.²⁰ However, few has been detailed about the relation between onset of PL and stroke. We therefore conduct a comprehensive search of the English literature from PubMed database. The PubMed database was searched from January 1993 through May 2010 for articles published in English with keywords such as *pathological laughing* and *pathological crying* combined with keywords such as *stroke* and *cerebrovascular events*. We found 33 reported cases of PLC after cerebrovascular disease in the recent 20 years (Table 1).^{4,11–13,21–32} One patient with subarachnoid hemorrhage¹³ and 3 patients lacking of a specified lesion or an onset interval were excluded.^{23,26} Notably, we found that there is a higher rate of a delayed onset of PLC after cerebrovascular events in patients with supratentorial lesions as compared with patients with brainstem lesions (78.6% vs 13.3%, $P = 0.02$ by χ^2 test). Delayed onset was defined as onset of PLC equal to or more than 1 week after cerebrovascular events. The mechanism why supratentorial lesions are associated with a higher rate of delayed development of affective disorders remains unclear. It is postulated that delayed-onset PLC after subcortical stroke was related to the prolonged recovery of cortical dysfunction until proper recognition to socioemotional trigger.³³ Otherwise, a more confined lesion in the brainstem may unleash the symptoms more quickly. However, this rare case that we presented was a delayed-onset PLC with pontine hemorrhage. We supposed that the relatively more extensive damage due to brainstem hemorrhage may result in its delayed onset of symptoms. In conclusion, our observations expand the current knowledge of treatment choices of PL caused by pontine lesions. Further large-scale controlled trials are warranted to evaluate the beneficial and differential effects of quetiapine on PL.

TABLE 1. Clinical Manifestations of Previous Reported Cases of PLC After Cerebrovascular Events

Author/Year	Age, yr/Sex	Lesion	Onset of PLC After Stroke	Treatment of PLC	Interval of Treatment Response
Wali ²¹ /1993	35/F	Left pontine infarct	4 d	N/A	N/A
Dootenbos et al ²² /1993	73/M	Left cerebellar hemorrhage	2 mo	N/A	N/A
Mukand et al ²³ /1996	62/M*	Recurrent stroke, not addressed	N/A	Setraline (50 mg/d)	1 week
	72/M*	Right MCA infarct	N/A	Setraline (25–50 mg/d)	4 days
Kim ²⁴ /1997	44/M	Right periventricular area infarct	5 d	N/A	N/A
	50/F	Left periventricular area infarct	3 wk		
	63/M	Right periventricular area infarct	1 yr		
	52/F	Right periventricular area infarct	1 yr		
	44/F	Left internal capsule infarct	4 mo		
	54/M	Right periventricular area infarct	Several weeks		
	51/M	Right periventricular area infarct	2 wk		
	63/M	Right posterior internal capsule infarct	2 wk		
	39/M	Left periventricular area infarct	3 wk		
	68/F	Left capsular-thalamic hemorrhage	1 wk		
	58/M	Left pontine infarct	Several days		
	51/M	Right pontine infarct	Immediate		
	36/M	Right pontine infarct	Immediate		
Derex et al ²⁵ /1997	55/M	Left internal capsule infarct	Immediate	Paroxetine (20 mg/d)	1 day
Jeret ²⁶ /1997	77/M*	Left pons and thalamus infarct	N/A	Fluoxetine (10–20 mg/d)	N/A
Tet and Sakamoto ²⁷ /1997	69/F	Left pontine infarct	Immediate	N/A	N/A
Larner ²⁸ /1998	18/F	Right midbrain infarct	Immediate	N/A	N/A
Parvizi et al ⁴ /2001	51/M	Pontine and cerebellar infarct	Immediate	N/A	N/A
Gondim et al ²⁹ /2001	62/M	Left pontine and cerebellar infarct	Immediate	N/A	N/A
Smith et al ¹² /2003	67/M	Left parietal lobe and basal ganglia hemorrhage	Immediate	N/A	N/A
Ramasubbu et al ¹¹ /2003	50/F	Large left MCA stroke	3–4 wk	Venlafaxine (75 mg/d)	Within 24 h
Dabby et al ³⁰ /2004	49/M	Left lower midbrain infarct	Immediate	Lamotrigine (50–100 mg/d)	1–2 wk
	59/M	Left lower midbrain infarct	3 mo	N/A	N/A
	64/F	Bilateral pontine infarct	5 d		
Kim et al ¹³ /2005	63/F	Left frontotemporal lobe and basal ganglia hemorrhage	2 mo	Mirtazapine (3.75–15 mg/d)	2 d
	64/F*	SAH at bilateral frontotemporal areas	Immediate	Mirtazapine (7.5–45 mg/d)	2 d
Møller et al ¹⁵ /2007	48/M	Left pontine infarct	4 d	Nortriptyline (50–100 mg/d)	1 day
	56/M	Multiple bilateral subcortical and pontine infarcts	2 yr	Reboxetine (4–8 mg/d)	<1 mo
Oh et al ³² /2008	80/F	Bilateral pontine infarct	Immediate	Citalopram (40 mg/d)	2 wk

* Excluded one case of subarachnoid hemorrhage, and the cases lack of a specified lesion or an onset interval. F indicates female; M, male; MCA, middle cerebral artery; N/A, not available; SAH, subarachnoid hemorrhage.

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