Pathological Laughter Caused by Frontal Glioblastoma —Case Report—

Satoshi TSUTSUMI, Yukimasa YASUMOTO, and Masanori ITO

Department of Neurological Surgery, Juntendo University Urayasu Hospital, Urayasu, Chiba

Abstract

A 60-year-old, right-handed female presented with episodes of pathological laughter and left hemiparesis. She had no history of traumatic brain injury, or neurological or psychiatric disease, and showed no signs of drug or alcohol abuse. Neurological examination found moderate left hemiparesis. Her face was symmetrical with intact emotional expression. The episodes of pathological laughter had become more frequent during the 3 months since the onset of hemiparesis, were elicited by non-specific, trivial stimuli, and lasted for a few minutes until she gained some control. Her personal and social behavior was entirely appropriate except for the outbursts of laughter. Cerebral magnetic resonance (MR) imaging revealed a 2.5 × 2.5 × 3 cm ring-enhanced mass in the subcortical area of the right frontal lobe associated with extensive perifocal brain edema. The hypothalamus, thalamus, internal capsule, brainstem, and cerebellum were unaffected. Functional MR imaging showed the tumor located mainly in the prefrontal area with the posterior limit involving the premotor cortex. She underwent total tumor resection. The histological diagnosis was glioblastoma multiforme. The pathological laughter and hemiparesis resolved within 2 weeks after surgery. Invasive tumor in the frontal lobe involving the prefrontal cortex and subcortical structure may cause pathological laughter, and can be cured by surgery.

Key words: pathological laughter, functional anatomy, glioblastoma

Introduction

Pathological laughter is defined as relatively uncontrollable episodes of laughter with no apparent motivating stimulus or inappropriate stimulus under normal conditions. Pathological laughter is associated with various brain disorders such as pseudobulbar palsy, subcortical and brainstem infarction and injury, tumor in the cerebellopontine region, multiple sclerosis, and amyotrophic lateral sclerosis. The brainstem is generally agreed to incorporate a final common pathway for laughter, integrating facial expression, respiration, and autonomic reaction, probably located in the dorsal area of the upper pons and midbrain, and connected to the periaqueductal gray matter, reticular formation, and cerebellum that automatically adjust the execution of laughter or crying to the cognitive and situational context. The expression of laughter is considered to depend on two partially independent neuronal pathways: the involuntary or emotionally activated system, involving the amygdala, thalamic/hypo- and subthalamic areas, and the dorsal/tegmental brainstem; and the voluntary pathway originating in the premotor/frontal areas, and passing through the motor cortex and pyramidal tract to the ventral brainstem, which controls the facial and respiratory muscles. However, pathological laughter caused by frontal lesions or pathology in the striatocapsular area has rarely been reported.

We describe a case of frontal glioblastoma as a cause of pathological laughter.

Case Report

A 60-year-old, right-handed female had demonstrated episodes of inappropriate and uncontrollable laughing for 3 months after suffering left hemiparesis. She had no history of traumatic brain injury, or neurological or psychiatric disease, and had no signs of drug or alcohol abuse.

Neurological examination found moderate left hemiparesis, more pronounced in the upper extremity. Increased reflexes were elicited in the left upper and lower extremities with more pronounced hyper-
reflexia observed in the latter. Testing of all sensory modalities found no apparent abnormalities. Her face was symmetrical with intact emotional expression. The status of all cranial nerves was intact with normal jaw and facial reflexes, and negative snout response, without spastic dysarthria. Her Mini-Mental State Examination score was 29/30. The episodes of pathological laughter had become more frequent during the 3 months, and immediately arose following non-specific and trivial stimuli, which were actually not funny to her or in the circumstances, and lasted uncontrollably for a few minutes. She was aware that her laughter was abnormal and felt embarrassed by the attacks and struggled to stop them. She explained that she had exert little or no control over the onset of attacks, but usually gained some control within a few minutes. She also noted that, in spite of the appropriate laughter, she felt happy or sad after the episode. Except for the outbursts of laughter, her personal and social behavior was entirely appropriate.

Cerebral magnetic resonance (MR) imaging revealed a $2.5 \times 2.5 \times 3$ cm ring-enhanced mass in the subcortical region of the right frontal lobe, located adjacent to the anatomical primary motor cortex, and associated with extensive perifocal brain edema involving the cingulate gyrus (Fig. 1). The hypothalamus, thalamus, internal capsule, brainstem, and cerebellum were unaffected. No concurrent vascular or other tumorous lesions, or findings of multiple sclerosis were recognized. Functional MR imaging using T1-weighted, gradient echo, echo planar imaging sequences with a 1.5-Tesla MR scanner (Excelart Vantage; Toshiba Corporation, Tokyo) identified the tumor located mainly in the prefrontal area with the posterior limit involving the premotor cortex (Fig. 2). During the finger-tapping task, the patient had not been administered tricyclic antidepressants, selective serotonin reuptake inhibitor, or lamotrigine before she underwent tumor resection. The tumor was totally resected under neuronavigation system guidance without additional postoperative neurological deficit (Fig. 3). Histological examination of the tissue with immunostaining using glial fibrillary acidic protein and vimentin (not shown) identified glioblastoma multiforme (Fig. 4).
Pathological laughter caused by frontal glioblastoma

Proliferative activity was assessed as 25% by MIB-1 immunolabeling.

Her pathological laughter and hemiparesis disappeared within 2 weeks after surgery. She was discharged after irradiation (fractionation of 5 × 2 Gy/week, total 60 Gy) synchronous with oral chemotherapy using temozolomide (150 mg/m² daily for 42 consecutive days) without recurrence of the laughter.

**Discussion**

In the present case, functional MR imaging showed the offending glioblastoma was located in the frontal subcortical area involving the premotor cortex. The coexisting perifocal brain edema was extensive and displaced the cingulate gyrus downward. In contrast, the hypothalamus, thalamus, internal capsule, brainstem, and cerebellum were not affected. Therefore, we considered that the affected premotor cortex contributed to the occurrence of pathological laughter via the voluntary pathway leading through the pyramidal tract to the ventral brainstem, and controlling the facial and respiratory muscles. The displacement of the ipsilateral cingulate gyrus by the tumor might also have modulated the abnormal laughter via the involuntary or emotionally activated system involving the paralimbic structures, thalamic and hypothalamic areas, and connecting to the dorsal brainstem. However, we could not determine the exact anatomical structure as the origin of the pathological laughter because of the extensive effects of the lesion.

Pathological laughter caused by frontal lesions or pathology in the striatocapsular area has rarely been reported. In this unique case of pathological laughter was associated with a frontal glioblastoma. Cases of pathological laughter presented after traumatic brain injury in the frontal lobe and successfully treated with lamotrigine. Lamotrigine, an antiepileptic drug, may be effective against pathological laughter induced by traumatic brain injury.

Highly selective serotonin reuptake inhibitor was effective for a patient sustaining pathological laughter with stroke, but not in a case after traumatic brain injury.

No consistent relationship between pathological laughter and psychiatric diseases such as mood or anxiety disorders has been established. The present patient noted that her laughter was abnormal, and she felt happy or sad after an episode. Her personal and social behavior was entirely appropriate other than the laughter. Considerable evidence that pathological laughter responds to treatment with antidepressants may also obscure the exact nature. Tricyclic antidepressants are generally accepted to help patients with pathological laughter. Our patient felt embarrassed by the attacks, indicating that pathological laughter can be socially disabling and requires appropriate management.

Serotonergic receptors are widespread in many brain regions, especially the paralimbic regions considered to be emotion-induction and emotion-effector sites. Serotonergic projections also extend to the cerebellum. Patients with stroke and pathological laughter respond to treatment with highly selective serotonin reuptake inhibitor, supporting the notion that serotonergic pathways are involved in the regulation of the neural circuits coordinating complex behavioral responses such as crying and laughing. In the present case, the pathological laughter disappeared postoperatively and did not recur, and the patient has been followed up without...
medication.

The exact mechanism of development remains unknown in the present case, but the tumorous lesion in the premotor and prefrontal subcortical areas was likely to be the cause of the pathological laughter. The present case also showed that pathological laughter induced by such pathology may be curable by surgical intervention. Further innovation and refinement in neuroanatomical, neurophysiological, and neuroimaging methods combined with more experience might solve this mysterious condition in the future.

References

4) Matsuoka S, Yokota A, Yasukouchi H, Harada A, Kadoya C, Wada S, Ishikawa T, Okuda S: Clival chor-

Address reprint requests to: Satoshi Tsutsumi, M.D., Department of Neurological Surgery, Juntendo University Urayasu Hospital, 2–1–1 Tomioka, Urayasu, Chiba 279–0021, Japan.

e-mail: shotaro@juntendo-urayasu.jp