Hypothalamic Lesions and Intermittent Explosive Disorder

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The authors present two cases of patients with craniopharyngiomas who meet the DSM-III-R criteria for intermittent explosive disorder. Episodes of rage developed before and/or after surgery for removal of the craniopharyngioma. Magnetic resonance imaging revealed hypothalamic-hypophyseal involvement. It is suggested that hypothalamic lesions played a major role in the development of aggressive behavior in both cases.

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Contemporary medical science has inherited a rich legacy from physicians of the nineteenth century and their attempts to relate abnormal behavior to abnormal brains.[1–3] Despite over a century's attention to the relationship between violent behavior and the brain, however, the debate continues, with no end in sight. One contemporary focus of this debate has been the syndrome of "episodic dyscontrol" or "intermittent explosive behavior."

This syndrome was first described in neurological patients with seizure disorders.[4–7] It also has been shown that a significant factor in violent behavior can be the presence of a brain tumor or loss of brain tissue in certain areas due to head injury, stroke, infection, or neurosurgery.[8–10] Some animal and human studies have revealed that outbursts of rage similar to intermittent explosive behavior may be caused by electrical stimulation of the amygdala, septal nuclei, or posterior hypothalamus.[11]

Superimposed upon the discussion about the etiology of intermittent, repetitive violence has been the debate about the diagnosis of intermittent explosive disorder. The debate has included the parameters of the diagnosis,[12] the usefulness of the concept,[13] and the relationship between the presence of definable organic lesions and the diagnosis (personal communication, DSM-IV Work

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In this article we present two cases of patients with craniopharyngiomas who meet the DSM-III-R criteria for intermittent explosive disorder. We do so to further illuminate the relationships between behavior punctuated by periods of episodic dyscontrol and lesions in the hypothalamo-hypophyseal region.

CASE REPORTS

Case 1. Patient A., a 21-year-old white male, was referred for neuropsychiatric evaluation because of frequent episodes of explosive behavior, most notably threats to cut himself with a knife or to kill his mother. He complained of depressed mood and insomnia. He also reported the periodic appearance of visual and auditory hallucinations before going to sleep. Periods of "spacing out" for 15 to 20 minutes at a time had been noted by family and friends.

Family history was significant for a father who suffered from alcoholism for many years. The patient's mother was twice admitted to a state hospital with the diagnosis of unspecified character disorder. The patient had three siblings, two of whom were considered to be of normal intelligence with no overt behavioral problems. The third sibling had been enrolled in a special education program, where he reportedly was doing well.

The patient, who lived with his mother during his early years, did not get along well with her and had to be placed in various foster homes, beginning at age 13.

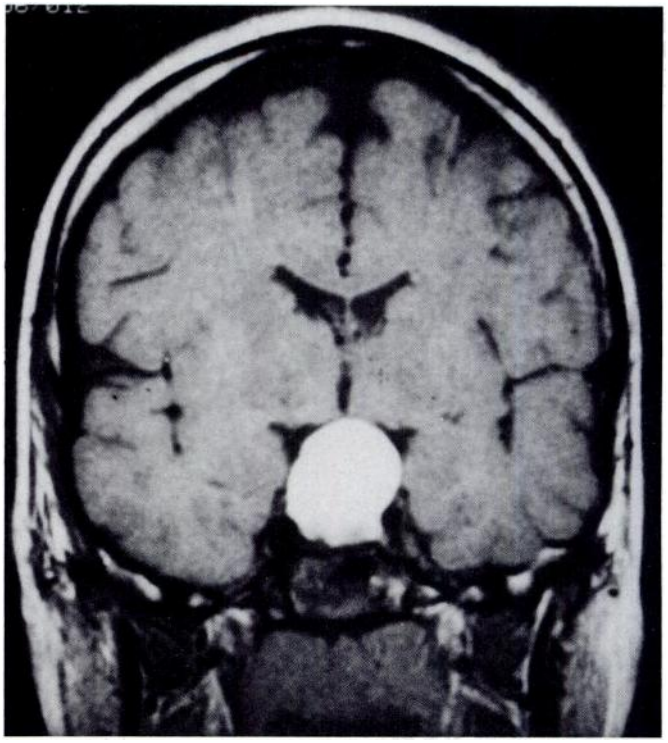
At age 16, the patient was admitted to a general hospital psychiatric ward following threats to kill himself with a knife. Two months prior to this admission, the patient had developed difficulties falling asleep, interrupted sleep during the night, and early morning awakening. The patient complained of "feeling down"; he noted a poor appetite and weight loss. He stated that he had seen "the face of the devil" when he was alone, most often just before sleep; the "devil" told him to hurt himself and "other bad things." Periods of "spacing out" had preceded the sleep difficulties by several months. An EEG was found to be within normal limits during this admission. The patient was discharged with the diagnosis of borderline personality disorder.

The patient's symptoms continued to worsen. Confrontations with his teachers led to his dropping out of the ninth grade. Shortly thereafter, he began living on the streets, unable to keep any steady job. Between the ages of 18 and 20, the patient had three admissions to Worcester State Hospital (WSH) from which he was discharged with the diagnoses of conduct disorder and/or atypical depression. He complained of visual and auditory hallucinations, depressed mood, and episodes of "spacing out." He presented with irritability, intermittent outbursts of assaultive behavior, insomnia, and weight loss. A decline in his IQ was noted (from the level of 120 at the age of 15) to a full scale of 87. When he was 20, during an admission to WSH, his progressive weight loss and complaints of dizziness and fatigue prompted a thorough medical evaluation.

The patient presented with polydipsia, increased thirst, polyuria, lack of pigmentation, and diabetes insipidus. Laboratory data included a blood sugar of 66, testosterone level of less than 20 ng/dl (normal limits 280–1100 ng/dl), cortisol level of 2.5 ng/dl at 8:00 A.M. (normal range 9–24 ng/dl), T4 of 4.0 ng/dl (normal limits 4.0–12.0 ng/dl), and free thyroxine index of 1.1 (normal range 1.4–3.7). Goldman visual fields demonstrated depression of the superior temporal fields in both eyes, suggestive of chiasmal compression. Magnetic resonance imaging (MRI) findings (Figure 1) were consistent with the presence of a craniopharyngioma expanding the sella and extending in the suprasellar direction to the chiasm, displacing the chiasm superiorly. There was neither evidence of extension into the cavernous sinus nor evidence of third ventricular obstruction.

The patient underwent a right frontal craniotomy with evacuation of a cyst from the suprasellar region. After surgery, the patient developed tonic-clonic seizures (controlled by phenytoin) and exacerbation of his diabetes insipidus. His psychiatric manifestations did not change. MRI showed the incomplete resection of the craniopharyngioma. A second operation had to be performed 5 months after the first in an attempt to complete the removal of the tumor. Follow-up MRI revealed an overall decrease in the size of the residual neoplasm within the sella region.

FIGURE 1. T2-weighted image showing craniopharyngioma before the surgery (Case 1).



However, the findings also suggested regrowth of a small amount of tumor within the posterior aspect of the sella region, within the inferior part of the original tumor. EEG showed moderate paroxysmal activity manifested as single spikes especially prominent at the left hemisphere leads.

After the second surgery, the patient's behavior remained unchanged. He continued to present with intermittent explosive episodes manifested as fights with other patients and assaults of staff members. The patient reported visual and auditory hallucinations and complained of depressed mood. He appeared to be tense and irritable. He was oriented to time, place, and person. Immediate recall of three words with 5-minute delay was preserved. However, remote memory was disturbed. Shifting of attention was also difficult. His blood pressure was 95/70, with a pulse of 80. There was no gynecomastia or galactorrhea. On general examination the paucity of facial and body hair was noted.

Treatment has consisted of replacement therapy: hydrocortisone, testosterone, and synthroid. Phenytoin has been used to control seizures. Attempts to use carbamazepine have failed because of hematologic side effects. The effects of haloperidol and imipramine have been inconclusive.

Case 2. Patient B., a 24-year-old white female, was referred for neuropsychiatric evaluation because of episodes of explosive behavior, including threats to start a fire, assaults on staff, and runs from her community residence. She complained of depressed mood; several suicide attempts had been recorded over a period of several years. The patient was overeating, and marked obesity was noted.

The patient's birth and childhood development were described as normal. Throughout elementary school, she was considered to be an honor student. She was noted to have a good relationship with her parents, her only sister, and her peers. No history of mental illnesses or drug or alcohol abuse was noted in the family.

At the age of 11 years, the patient developed growth retardation and weight loss. One year later, further examination revealed a benign tumor in the hypophyseal-hypothalamic region, which was removed through right frontal craniotomy. The tumor was a craniopharyngioma. About 4 months later, the patient developed signs of hypopituitarism, including diabetes insipidus, hypoadrenalism, and hypothyroidism. She started to eat excessively and became obese. Clumsiness and ataxia also were noted. The patient's behavior drastically changed. She became intermittently assaultive, was destructive to property, and threatened to inflict self-injury.

Following these episodes of dyscontrol, the patient was calm and exhibited guilt over the violence. Her cognitive functioning remained in the normal range. Approximately 6 months after the craniotomy, a shunt was placed into the right lateral ventricle in attempts to relieve the increasing pressure from the progressive hydrocephalus. Gait and motor functions markedly improved after this surgery, but the shunt did not produce any positive effects on the patient's behavior.

The patient returned home, but, due to her behavior problems, she never returned to the public school system. She subsequently was placed in a number of psychiatric and residential treatment facilities without apparent improvement, despite active behavioral therapy and trials of many medications, including neuroleptics, antidepressants, and substitute hormonal therapy.

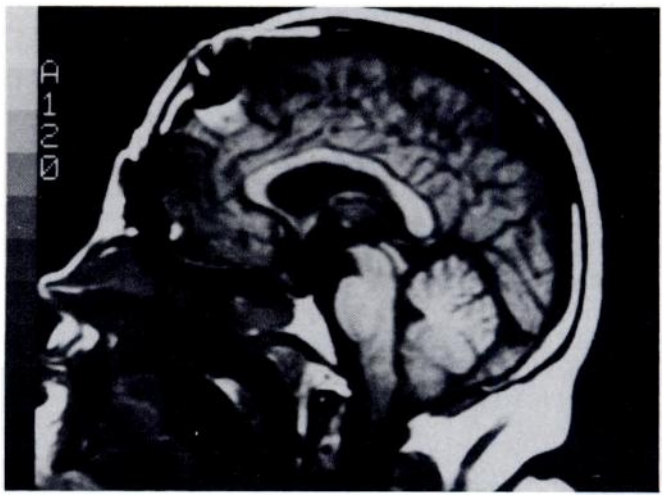
At the age of 24, an MRI (Figure 2) revealed loss of definition of the sella, pituitary gland, and pituitary stalk, and prominence of the suprasellar cistern. The third ventricle was patulous in configuration. No residual tumor was identified. There was some increased T2 signal intensity under the right orbitofrontal region at the base of the skull, probably related to the prior surgery. EEG recorded gross abnormalities manifested as high amplitude sharp waves, especially prominent at the temporo-occipital leads. No history of seizure was noted (including the period before and after surgery).

In view of the EEG findings, trials with carbamazepine were started. On the dosage of 200 mg tid, the patient's behavior markedly improved. It was eventually possible to discontinue all neuroleptic and antidepressant medications and to discharge the patient to a community residential program.

DISCUSSION

Intermittent explosive behavior appears to be related to lesions of the hypothalamo-hypophyseal axis caused by growth of a craniopharyngioma in Case 1 and surgery for its removal in Case 2. Craniopharyngioma is a benign congenital tumor believed to grow from the remnants of Rathke's pouch, the so-called cell rest at the junction of the infundibular stem and the pituitary gland. It reaches the diameter of three to four centimeters and becomes cystic at that time.[14] The tumor usually lies above the sella turcica, depressing the optic chiasm and producing chiasmal field defects, as seen in Case 1. The tumor may grow within the sella, compressing the pituitary body

FIGURE 2. T2-weighted image showing changes after the surgery. No residual tumor may be identified (Case 2).



and extending up into the third ventricle, causing hypopituitary-hypothalamic derangement. The presenting syndrome often takes the form of hypopituitarism, with deficiencies of growth hormone, thyrotropin, ACTH (adrenocorticotropic hormone), and gonadotropin. The presence of diabetes insipidus occurs with hypothalamic involvement; deficiencies in antidiuretic hormone (ADH) release may be caused either by the massively enlarged anterior pituitary lesion or by retrograde degeneration of the neurons of the supraoptic nuclei. Other clinical findings described in patients with craniopharyngioma include mental illness and memory defects.[15] Malamud[16] presented three cases with craniopharyngiomas, respectively diagnosed as schizophrenia, manic excitement, and psychoneurosis. Killefer and Stern[17] reported a case in which "episodic savage behavior" and "rage spells" developed several weeks after total removal of a craniopharyngioma.

Episodes of assaultiveness and rage outbursts seemed to be direct manifestations of tumor growth in the hypothalamo-hypophyseal region in Case 1. The second case was characterized by the development of behavioral problems several months after the complete removal of the craniopharyngioma, probably as a sequela of the extensive hypothalamic damage produced by the surgery. In both cases, the craniopharyngioma grew toward the hypophysis as well as toward the hypothalamic region.

As to the extent of the lesion within the hypothalamic region, the findings in Case 2 point to the more extensive involvement of the hypothalamic-hypophyseal region occurring before the intermittent explosiveness developed. Clinical manifestations antedating the surgery included growth retardation *without* concomitant behavior problems. Several months after the complete removal of the craniopharyngioma, the patient developed episodes of rage outbursts and confusion, as well as neuroendocrinological signs of a more severe and extended hypothalamo-hypophyseal lesion (diabetes insipidus, hypoadrenalism, and hypothyroidism). Similar signs of hypopituitarism were observed in Case 1 before surgery. The difference between the two cases helps to explain the finding that in many cases with craniopharyngioma, when the lesion is less extensive, behavior problems are absent.

Findings of hypothalamic involvement in patients with intermittent explosive behavior may be compared with the previously reported development of ferocious behavior and hyperphagia in cats in response to electrical stimulation of the posterior lateral hypothalamic region.[11] The association of episodes of rage and hyperphagia has been described in patients with hypothalamic tumors in the region of the third ventricles. Reeves and Plum[18] described a young woman who developed outbursts of violence that consisted of hissing, biting, scratching, and throwing objects at attendants, and who experienced visual and auditory hallucinations. The patient also presented with diabetes insipidus, bulimia, and obesity. The patient died 2 months after exploratory craniotomy. The autopsy confirmed the presence of a hamartoma that mainly occupied the ventro-medial hypothalamic nuclei. Haugh and Marnesbery[19] reported a 26-year-old woman with intermittent aggressive behavior, hyperphagia, obesity, and hypopituitarism. The patient died from acute pancreatitis. Autopsy revealed a low-grade astrocytoma in the third ventricle occupying the medial hypothalamus with encroachment to the anterior-medial and posterior hypothalamus. Recently, Flynn et al.[20] presented another case with intermittent explosive behavior associated with damage to the ventro-medial hypothalamus.

Animal and human studies point to the role of the hypothalamus in the production of the response needed for preparation and execution of aggressive behavior. The response includes a rise in blood pressure, tachycardia, and pupillary dilation; it may be elicited by stimulation of a so-called "ergotonic triangle" formed in the posterior hypothalamus by the mid-point of the intercommissural line, the rostral end of the aqueduct, and the anterior border of the mamillary body. At one point, the ergotonic triangle was surgically destroyed for the treatment of aggressive behavior.[21] These operations, however, have been abandoned because of ethical controversies.

There are contradictions between the reported diminution of aggressive behavior following hypothalamic stereotaxic surgery[21] and the development of intermittent explosive behavior in our case and in other cases with hypothalamic tumor or injury.[16,18–20] These contradictions may be related to whether or not there is partial preservation of the posterior hypothalamus. It is possible that tumor growth or development of scars after tumor removal interrupts the connections of the posterior hypothalamus with the other parts of the limbic system that normally inhibit the release of programs of violent behavior by the posterior hypothalamus. That disconnection may produce disinhibition of violent behavior.

Inhibitory impulses on the posterior hypothalamus also could be diminished by paroxysmal activity in our two cases. A seizure disorder of the generalized tonic-clonic type was recorded in Case 1 after surgery. In Case 2, prominent subclinical paroxysmal activity was recorded on EEG. Paroxysmal activity probably spread to the posterior-lateral hypothalamic region, facilitating the release of programs of violent behavior already uninhibited by the disconnection of the posterior hypothalamus from other parts of the limbic system.

Our two cases, with aggressive behavior due to the hypothalamic involvement, had significant differences in their psychiatric manifestations as compared to the group of five violent patients with temporal lobe lesions previously described by one of us (J.T.).[10] Persecutory delusions were present in three out of five patients of the violent temporal group, while neither of our two cases exhibited any sign of delusions. On the other hand, hallucinations were present in our two cases, primarily visual in nature, with mainly hypnagogic appearance in Case 1. This type of hallucination was described by Lhermitte under the term "peduncular hallucinosis"[22] and may be a result of the influence exerted by the tumor in the hypothalamo-hypophyseal region on the adjacent peduncular areas. Hallucinations were observed in only one of the five violent patients with the anterior-inferior temporal lesion.[10] Cognitive decline was much more prominent in the temporal lobe group, with the range of decline from low level IQs of 57 to 63 to severe dementia; this was the case with the two patients with craniopharyngioma, who maintained normal (Case 2) or who declined to the borderline level of intelligence (Case 1).

Affective disturbances seemed to be similar in both groups, manifesting as depressed mood and affective instability. Neuroendocrinological abnormalities, typical for panhypopituitarism, were present in patients with craniopharyngioma and completely absent in the temporal group, stressing the possible role of these abnormalities in the development of intermittent explosive behavior in the two cases of craniopharyngioma.

The possible connection of violent outbursts with some of the abnormalities in the hypothalamo-hypophyseal axis has been previously described. Episodes of rage outbursts and violent behavior were elucidated in patients with low glucose values on the glucose tolerance test,[23,24] with hyperphagia caused by hypothalamic tumors[18,19] and with high testosterone[25] or low progesterone levels.[26]

In animals, low glucose levels and hyperphagia may be in some way directly related to aggressive behavior because hunger usually leads to the search for food and to the aggression that is needed in order to obtain the food. In this case, the hypothalamus mediates the response through somatic signals such as the need to get food. Certainly, a similar mechanism would be more sophisticated in humans and would be controlled by the various guidance programs in the upper parts of the limbic and frontal lobe systems. However, the most primitive mechanism seen in animals may surface in humans when the presence of hyperphagia and hypoglycemia facilitates the development of rage outbursts produced by the disinhibited posterior hypothalamus or other parts of the limbic system that are both disconnected from the inhibitory influence of the hypothalamus and stimulated by seizure activity.

In contrast, in violent patients with anterior temporal lesions, the intermittent release of violent programs does not seem to be connected with the feedback of somatic needs and may be related to the distorted perception of danger or humiliation in such cases. Certainly, mechanisms of violence in patients with focal brain pathology require further study on a larger number of cases, including the application of special neuropsychological techniques for the measurement of prosody or comprehension of emotional language.

Some might argue that a disturbed family environment contributed to our patients' explosive behavior. However, that behavior only reached a clinically significant degree in Case 1 with the development of the craniopharyngioma; the patient's three siblings had not been characterized as behaviorally disturbed. In Case 2, the patient was described as a normal child from a good family environment until the development of the prominent posterior hypothalamic lesion following the removal of the craniopharyngioma.

Finally, it has to be stressed that slowly progressive, often benign, brain tumors may produce clinical manifestations resembling major mental illnesses. Patients with such manifestations may reside in psychiatric institutions without appropriate evaluation and treatment. In Case 1, the patient carried the diagnoses of conduct disorder and borderline personality disorder for several years before the craniopharyngioma was found. It also should be noted that lesions in the hypothalamic region may result in intermittent explosiveness in patients with symptoms of major mental illnesses from causes other than brain tumors.

Intermittent explosive behavior/dyscontrol syndromes remain troubling to patients, practitioners, and the public. We have presented two cases of craniopharyngioma and aggressive dyscontrol in an attempt to further the understanding of this often puzzling and frightening manifestation of aggression. Further studies of similar cases with the use of modern brain imaging techniques should prove fruitful in obtaining a better understanding of the diagnosis, brain mechanisms, and treatment of patients with such behavior.

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