Altered Behavior Associated with Damage to the Ventromedial Hypothalamus: a Distinctive Syndrome

FREDERICK G. FLYNN, JEFFREY L. CUMMINGS, and UWAMIE TOMIYASU

Neurobehavior Unit, and Laboratory Service (Neuropathology), West Los Angeles Veterans Administration Medical Center; Departments of Neurology and Psychiatry and Biobehavioral Sciences, UCLA School of Medicine, Los Angeles, California, 90073; and U.S. Army AMEDD Student Detachment, Academy of Health Sciences, Ft. Sam Houston, Texas.

An adult manifested a tetrad of neurobehavioral findings consisting of episodic rage, emotional lability, hyperphagia with obesity, and memory impairment with intellectual decline following surgical removal of a craniopharyngioma. Post-mortem investigation of the topography of the lesion as well as review of previously reported cases suggest that this tetrad represents a specific neurobehavioral syndrome referable to damage to the ventromedial hypothalamus.

A plethora of experimental studies demonstrate behavioral changes in animals after lesioning of specific areas of the hypothalamus. Behavioral alterations have also been described in humans with pathology in this region, but there is a paucity of studies correlating specific behaviors with the topography of lesion sites. We report clinical and pathological studies of an adult with a distinct tetrad of severe behavioral abnormalities arising after surgical removal of a craniopharyngioma that had invaded the hypothalamus. The pertinent literature is also reviewed.

Case Report

A 32-year-old right handed man presented with headache, neck pain, dizziness, hypersomnolence, and decreased appetite. Initial neurological examination revealed a blunted affect and an incongruous left inferior quadrantanopsia. Computerized tomography (CT) demonstrated an enhancing suprasellar mass, and arteriography confirmed the presence of a large avascular lesion in the hypothalamic area. A right temporal craniotomy and tumor excision were performed. Histologic studies revealed the mass to be a craniopharyngioma. Postoperative CT demonstrated an operative defect in the right hypothalamic region without evidence of residual tumor. The patient then received a total of 5000 rads of cranial radiation over a 5-week period.

Within one month of operation the patient developed panhypopituitarism, requiring supplementation with arginine vasopression, prednisone, and thyroid hormone. He was also noted to have impulsive agitated behavior.

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alternating with childlike whining and crying. He began to eat excessively, had difficulty with memory, and became depressed. The patient was placed on desipramine for depression and haloperidol for agitation. Within 10 months of surgery the patient's agitation had evolved into intermittent episodes of impulsive violence. During these times the patient engaged in verbal abuse of family, hospital staff, and other patients. Over the ensuing one-and-a-half years the patient impulsively destroyed the contents of a garage, a pool table, door windows (including one that was reinforced by wire), door bolts, bedroom windows, water fountains, fire extinguishers and numerous pieces of furniture. Caretakers were often injured during attempts to intervene, although the unprovoked violence was rarely directed specifically at individuals. Various combinations of haloperidol (to 120 mg/d), chlorpromazine (to 3000 mg/d), lithium carbonate (to 1200 mg/d), and propranolol (to 320 mg/d) failed to control the violent outbursts. During a one-and-a-half year period the patient required physical restraint by tying all 4 limbs on over 30 occasions. Hyperphagia led to a weight gain of nearly 100 pounds. Attempts to restrict his caloric intake often precipitated violent outbursts.

Mental status examination 2 years after the surgery revealed an alert patient whose affect was flat and whose psychomotor speed was slightly slowed. Digit span was 6 forward and 3 backwards. Memory testing revealed an immediate recall of 3 out of 3 words, but none of the 3 were recalled after 3 minutes. The patient's inability to learn was corroborated by nursing personnel and housestaff. In addition to the difficulty remembering new information, he was unable to adapt to new routines or retain instructions. Remote memory remained intact with the exception of a brief period of retrograde amnesia preceding the patient's surgery. In addition to his severe amnesia, the patient also had minor deficits of calculation, word list generation, abstract thinking, and frontal systems tasks. The patient's general neurologic examination demonstrated an incongruous left inferior quadrantanopsia, a flattened left nasal-labial fold, left pronator drift, and a left plantar extensor response. A CT scan (Fig. 1) demonstrated right temporal lobe as well as right hypothalamic defects, and the third ventricle was slightly enlarged. There was no radiologic evidence of recurrent tumor.

The patient became increasingly immobile due to excessive weight and hypersomnolence. He was found pulseless and apneic and attempts to resuscitate him failed. The cause of death was massive bilateral pulmonary emboli with acute cor pulmonale and pulmonary edema. Examination of the brain revealed a 4.5 x 3.5 cm surgical defect in the right temporal lobe. This lesion did not involve the amygdala or parahippocampal gyrus. There was a 1.8 x 1.2 x 1.5 cm cavity in the infundibular area. It involved most of the right rostral hypothalamus as well as the left ventromedial hypothalamus (Fig. 2). The following specific nuclei were involved: ventromedial, anterior, paraventricular, dorsomedial, supraoptic, lateral, tuberal, and posterior. The latter 4 nuclei were less affected than the anterior and medial groups. There was also involvement of the descending columns of the fornix.
ALTERED BEHAVIOR AND VENTROMEDIAL HYPOTHALAMUS

Fig. 1. Post-surgical CT scan demonstrates right temporal lobe and right hypothalamic defects with enlargement of the third ventricle.

(particularly on the right). The post-surgical cavity extended superiorly into the right internal capsule, the massa intermedia, and the dorsal medial thalamus. The right lateral and third ventricles were enlarged. Microscopically, the tissue surrounding the cavity consisted of a gliotic scar. Chronic inflammatory cells were seen in the thalamus and medial globus pallidus. The pituitary was small but intact. No recurrent tumor or radiation-induced necrosis were seen.

Discussion

Direct invasion of the hypothalamus has been reported to produce endocrine, neurologic, and behavioral abnormalities in various combinations (Bauer, 1954; Bray and Gallagher, 1975). However, direct invasion of the hypothalamus by tumour producing the tetrad of (1) episodic rage, (2) emotional lability, (3) hyperphagia with obesity, and (4) intellectual deterioration have been described in only four previous cases (Table 1).
Fig. 2. Coronal section of the brain demonstrates extensive right hypothalamic and left ventromedial hypothalamic damage. There is involvement of the right thalamus and internal capsule. Surgical damage to the right temporal lobe is also visible.

(Collins, 1942; Haugh and Markesberry, 1983; Killeffer and Stern, 1970; Reeves and Plum, 1969). In the current patient these features were the most conspicuous aspects of the clinical presentation. While present in the 4 cases noted above, the tetrad of behavioral findings was not emphasized or recognized as a specific syndrome with localizing significance. In all patients in whom the neurobehavioral syndrome discussed here was described, the principal site of brain injury involved the ventromedial hypothalamic nuclei.

Bauer (1954) reviewed 60 cases of hypothalamic lesions previously reported in the literature. Fifty-one of these cases were due to tumors. Twenty-one of the patients had associated psychiatric manifestations, and behavioral changes represented the initial symptoms in 7. In this series, the psychiatric features observed included rage, emotional lability, or abnormal sexual behavior. Another retrospective study (Bray and Gallagher, 1975) of 69 patients with hypothalamic obesity disclosed 20 per cent to have associated behavioral changes, but the nature of these changes was not discussed. These large reviews suggest that behavioral alterations are common with hypothalamic lesions, but that the specific syndrome discussed here is relatively infrequent.

The 4 components of the neurobehavioral syndrome have been des-
cribed primarily in conjunction with hypothalamic injury, but may also occur with lesions in other areas. When all 4 behavioral features are simultaneously present, a lesion in the ventromedial hypothalamus is almost invariably found. Episodic rage due to hypothalamic lesions has been reported in both animal and human studies. Hess (1956) demonstrated that stimulation of the perifornical area of the hypothalamus made docile animals enraged. Bard (1928) showed that the expression of rage was independent of the cortex, occurring even when all tissue rostral to the posterior hypothalamus was removed. Akert (1959) suggested that the ventromedial hypothalamus suppresses other hypothalamic regions, and lesioning these nuclei releases inhibition and produces rage behavior. All reported human cases of episodic rage due to tumors of the hypothalamus involved the ventromedial nuclei (Table 1).

In addition to rage attacks, the current case had marked oscillations between inappropriate laughter and crying, as well as occasional childlike remorse after his violent outbursts. This lability has been observed previously in patients with ventromedial nuclear involvement (Reeves and Plum, 1969; Killeffer and Stern, 1970; Beal et al., 1981). The patient lacked signs of pseudobulbar palsy and the changes in affect reflected emotional fluctuations and impaired mood control.

The ventromedial hypothalamic region has also been implicated in feeding behavior. Bilateral lesions of this region lead to excessive eating, whereas stimulation results in starvation (Akert, 1959). The production of hypothalamic hyperphagia is not limited to lesions of the ventromedial area (Rabin, 1972; Gold, 1973). Gold (1973) suggested that lesions in the ascending noradrenergic bundle rostral to the ventromedial hypothalamus can produce hyperphagia; Ahlskog et al. (1975) hypothesized that these two areas play independent roles in feeding behavior and that simultaneous lesions in both result in more extreme hyperphagia than a lesion in either the noradrenergic bundle or ventromedial nuclei alone.

Another cardinal element of this syndrome is intellectual decline. Memory loss is the most prominent feature. The current patient demonstrated an amnestic pattern of memory disturbance with poor ability to learn new information, retrograde amnesia, and intact recollection of remote material. Similar memory disorders have been described in the patients reported previously with similar syndromes (Table 1). Patients with more extensive brain involvement may develop dementia during the course of their illness (Reeves and Plum, 1969; Killefer and Stern, 1970; Beal et al., 1981). Lesions of the mammillary bodies, fornix, dorsomedial nucleus of the thalamus, and hippocampus have all been implicated in the production of amnestic syndromes. The descending columns of the fornix are especially susceptible to damage when the ventromedial nuclei are involved. This was noted in the present patient as well as several others (Reeves and Plumb, 1969; Haugh and Markesbery, 1983). Although involvement of mammillary bodies and fornices may be responsible for the memory deficit, a primary role in memory for the ventromedial hypothalamus itself has been postulated (Beal et al., 1981; Reeves and Plum, 1969). Animal studies have
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<td>Hypothalamic involvement</td>
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<td>Most affected:</td>
<td>Right: VM, ANT, PV, DM</td>
<td>Craniopharyngioma</td>
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<td>Left: VM</td>
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<td>Less affected:</td>
<td>Right: SO, LAT, TUB, Post</td>
<td>All hypothalamic nuclei</td>
<td>Bilateral: VM, DM, SO (caudal aspect only)</td>
<td>All hypothalamic nuclei except MB (intact remnants)</td>
<td>Most affected: Right: VM, DM, PV, ANT, MED, SC</td>
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<td>Left: Post</td>
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<td>Other structures involved</td>
<td>Right: IC, DMT, MI, descending columns of fornix</td>
<td>Floor of the third ventricle</td>
<td>Descending columns of fornix (bilaterally)</td>
<td>Third ventricle LT, AC Right fornix</td>
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| Left: Descending columns of fornix (only slightly involved) | }
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<td>Diabetes insipidus</td>
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<td>Amenorrhea</td>
<td>Hyperglycemia</td>
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<td>Hypothermia</td>
<td>Reversal of sleep-wake cycle</td>
<td>Visual hallucinations</td>
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**Code:**  
AC = anterior commissure; ANT = anterior; DM = dorsomedial; DMT = dorsomedial thalamus; IC = internal capsule; LAT = lateral; LT = lamina terminalis; MB = mamillary bodies; ME = median eminence; MED = medial; MI = massa intermedia; PO = preoptic; POST = posterior; PV = paraventricular; SC = suprachiasmatic; SO = supraoptic; TUB = tuberal
demonstrated that amygdalofugal pathways to the ventromedial hypothalamus are important in the acquisition of new memory and lesions in these regions may contribute to the memory deficit (Gold and Proulx, 1972; Schwartz and Teitelbaum, 1974).

Treatment of the behavioral manifestations associated with ventromedial hypothalamic lesions has been largely unsuccessful. Large doses of neuroleptics, beta-adrenergic blocking agents, and lithium carbonate failed to alter the behavior of the current patient. In some patients, these agents—alone or in combination with antidepressants, benzodiazepines, or testosterone antagonists—have ameliorated the aggressive episodes (Sheard, 1984; Goldstein, 1974). Psychotherapy and behavioral modification approaches have consistently failed to improve behavior (Goldstein, 1974). Pharmacologic studies in animals suggest that rage and appetite are mediated by cholinergic mechanisms and can be manipulated by cholinergic agonists and antagonists (Myers, 1964; Smith et al., 1970; Yoburn and Glusman, 1984). Such observations may eventually lead to more efficacious treatment. Amygdalotomy (Naraboyashi, 1963; Heimburger et al., 1966), posterior hypothalamotomy (Sano et al., 1970), and thalamotomy (Andy and Jurko, 1972) have been shown to diminish aggressive behavior in animals and humans. While controversial as therapeutic interventions, their success attests to the importance of these structures in mediating aggressive behavior.

Other abnormalities exhibited by the current patient and others with hypothalamic lesions include diabetes insipidus, hypothyroidism, hypoadrenalism, sleep abnormalities, and disturbances of temperature regulation. Diabetes insipidus is seen with lesions of the supraoptic and paraventricular complex as well as the infundibular stalk (Rodeck, 1967). Interference with thyroid releasing factor due to lesions of the anterior hypothalamus as well as reduction in adrenocorticotropic hormone production from injury to the ventral hypothalamus may result in hypothyroidism and hypoadrenalism, respectively (Reichlin, 1963). Abnormalities of sleep have been reported with lesions of the basal diencephalon, and Jouvet (1967) proposed that this region subserves behavioral arousal. Poikilothermia has been produced by bilateral caudal and lateral hypothalamic lesions, and heat loss can be interrupted by lesions in the preoptic or lateral anterior hypothalamus (Akert, 1959).

Behavioral disturbances associated with hypothalamic tumors have previously been reported, but their importance has been underemphasized. Behavioral disturbances may be the initial manifestations of hypothalamic involvement and may dominate the clinical syndrome. The tetrad of episodic rage, emotional lability, hyperphagia with obesity, and mental impairment represent a specific neurobehavioral syndrome associated with hypothalamic dysfunction. Evidence from this case as well as those previously reported suggests that when this tetrad is present the ventromedial hypothalamus is invariably involved.
ACKNOWLEDGEMENTS

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