

Basal Forebrain Infarction

A Clinicopathologic Correlation

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● Following the repair of a ruptured anterior communicating artery aneurysm, a patient had a severe anterograde amnesia with sparing of other intellectual functions, apathy and loss of volition, altered arousal, and partial diabetes insipidus. Postmortem examination of the brain revealed bilateral destruction of the septal gray, nucleus accumbens, and nucleus of the diagonal band of Broca. Also involved in the lesion were inferior portions of the anterior limb of the internal capsule and globus pallidus. Discrete, microinfarcts were present in the paraventricular hypothalamic gray. Long-term therapy with desaminoarginine vasopressin nasal spray had no effect on the patient's neuropsychologic deficits.

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The behavioral changes and amnesia which may complicate surgery for ruptured anterior communicating artery (ACoA) aneurysms^{1,2} have not previously been correlated with the underlying brain lesion(s). The clinical and pathological findings in a patient who suffered such complications are described in this article.

REPORT OF A CASE

A previously healthy 37-year-old man presented with a grade 2¹³ subarachnoid hemorrhage (SAH). Angiography showed

an ACoA aneurysm. The proximal (A1) segment of the right anterior cerebral artery could not be demonstrated. Fourteen days later, during which time he remained in a stable condition with normal mentation, the aneurysm was clipped and wrapped through a right frontal craniotomy. A global confusional state in the immediate postoperative period resolved after a few days, leaving him with an altered personality and an anterograde amnesia, which persisted unchanged until his death five years later.

Premorbidly, he had been friendly, outgoing, and energetic. After surgery, he was apathetic and withdrawn. He lacked his usual spontaneity and seemed to find difficulty with the initiation of any form of activity. He experienced daytime drowsiness and slept excessively. His appetite, libido, and nocturnal sleep pattern were unchanged. In superficial conversation, he appeared normal, but results of a clinical mental state examination revealed blunted affect, disorientation to time and place, defective short-term memory, patchy loss of remote memories, and a tendency to confabulate. Immediate recall was preserved and he was able to interpret proverbs. He retained some insight into his memory deficit, frequently complaining of "confusion." There was no thought disorder or language disturbance. On returning home, he could not safely be left alone and he required supervision in the personal activities of daily living. He frequently forgot whether he had bathed, shaved, or eaten, so that when left to his own devices, he might repeat these activities six or seven times a day. He was unable to return to work as a high-school science and physical education instructor.

In addition to these neuropsychologic disturbances, he also suffered from partial neurohypophyseal diabetes insipidus (DI)¹⁴ which was treated with 1-desamino-8-D-arginine vasopressin (dDAVP) nasal spray. On several occasions, he was readmitted to the hospital with hallucinations,

generalized seizures, asterixis, myoclonus, and diffuse slow-wave activity on electroencephalography (EEG). These encephalopathic episodes were associated with either hyponatremia or hypernatremia and cleared with correction of the metabolic aberrations, leaving his permanent deficits apparently unchanged. It was during one of these episodes that he died of pneumonia.

Neuropsychologic Assessment

The patient underwent formal neuropsychologic assessment at six months and three years after surgery.

During the first evaluation, the patient's behavior suggested fairly abrupt fluctuations in his level of arousal. At one point during the interview, he might appear sluggish, slightly disoriented, and poorly motivated; but minutes later, he would approach a task briskly and complete it very efficiently. He reported that he continually felt as though he had just awakened. He could relate in a socially normal fashion at any given time, but could not recall anything that had been said to him a moment earlier.

The Montreal Neurological Institute (MNI) Test Battery¹⁵ was administered. He performed within normal or near-normal limits in all areas assessed, except for memory, which was profoundly impaired. The Wechsler Adult Intelligence Scale (WAIS)¹⁶ Verbal, Performance and Full Scale IQs were 115, 104 and 111 respectively, suggesting mild impairment of nonverbal intellectual abilities. Verbal fluency was within normal limits,^{17,18} as were language functions,^{19,21} and left-right orientation.²² Construction, drawing, and perceptual analytic abilities appeared essentially intact, as evidenced by an average score on the WAIS Block Design subtest, adequate drawings of visualized objects,²³ and an accurate copy of the Rey-Osterreith Complex Figure.²⁴ Concept formation was within normal limits on Milner's²⁵ modification

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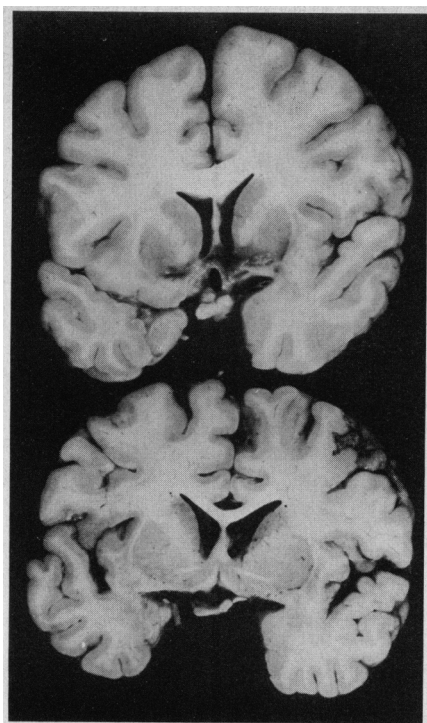


Fig 1.—Top, Coronal cut of cerebrum at level of olfactory trigones showing necrosis in region of basal forebrain. Bottom, Coronal cut of cerebrum immediately caudal to necrotic lesion showing preservation of subcommissural and postcommissural gray.

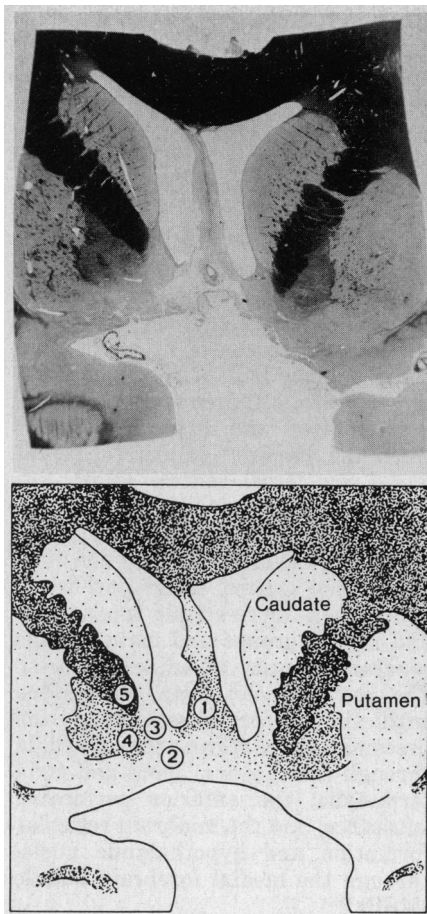


Fig 2.—Top, Histologic section at level of lesion showing cystic necrosis and adjacent zone of gliosis involving areas labeled in diagram (bottom) as follows: (1) precommissural or septal gray; (2) nucleus of the diagonal band of Broca; (3) nucleus accumbens; (4) rostroventral portion of globus pallidus; and (5) ventral segment of anterior limb of internal capsule.

evaluation. During the neuropsychologic assessment, his affect was very impassive. He demonstrated no spontaneous speech, but was alert and socially responsive when directly addressed. He could not spontaneously report aspects of his recent history but, when cued, he could recall and discuss incidents. He would willingly reply to the same question repeatedly, without apparent awareness that he had answered it before. He was cooperative and seemed well-motivated once engaged in a task. External stimuli, such as the sound of a distant siren, seemed to precipitate brief episodes of acute alarm, tremulousness, and profuse perspiration. His guardian reported that similar episodes would occur quite frequently during the day, often with no apparent provocation. Fluctuations in arousal of the type observed during the first assessment were not evident.

Retesting with the MNI Battery produced results virtually identical to those obtained 28 months earlier, except for poorer performances on digit span (eight forward, three backward) and concept formation. On the Wisconsin Card Sorting

Test he achieved only three categories, indicating significant impairment.^{26,29} Moreover, he produced almost twice the number of perseverative errors this time, especially in the second half of the test. This suggests that his ability to form and shift concepts was intact, but that he was experiencing difficulty in maintaining purposive behavior over time. These abnormalities were not present 28 months earlier, and may represent the subtle sequelae of repeated episodes of metabolic encephalopathy.

Neuropathologic Findings

External examination of the brain showed hemosiderin staining of the right gyrus rectus, the paraolfactory areas, and the suprasellar cistern. The A1 segment of the right anterior cerebral artery was absent. The left A1 segment gave rise to both distal anterior cerebral arteries, and at its bifurcation, there was a 6 to 7-mm berry aneurysm with a Yasargil clip and wrapping of acrylic material. There was a very small area of old hemorrhagic necrosis in the aneurysm bed. A coronal cut of the cerebrum made through this region, which was at the level of the olfactory trigones (rostral to the anterior commissure and lamina terminalis), revealed the center of a cystic necrotic area in the precommissural gray (Fig 1, top). Two large, 1.0-cm thick tissue blocks, that included the entire rostrocaudal extent of this lesion, were hand-processed for serial paraffin sections. It was noted that the most caudal extent of the lesion spared the anterior commissure and the postcommissural gray, ie, the nucleus basalis of Meynert (Fig 1, bottom).

Serial histologic sections defined the structures involved by the necrosis as follows: the precommissural gray (also called septal gray or paraolfactory area of Broca); nucleus of the diagonal band of Broca; nucleus accumbens; a small rostroventral portion of the globus pallidus; and a ventral segment of the anterior limb of the internal capsule (Fig 2). The lesion, while almost symmetrical, was slightly more extensive on the right. Sections through the hypothalamus showed two small necrotic lesions affecting only the paraventricular gray. The remainder of the brain was unremarkable; sections taken from the thalamus, hippocampi, caudate nuclei, globus pallidus (remote from the lesion), putamen, four areas of cerebral cortex, midbrain, pons, and cerebellum were histologically normal.

COMMENT

The basal forebrain damage in this patient presumably resulted from the inadvertent sacrifice of perforating branches of the proximal anterior cerebral and anterior communicating arteries³⁰⁻³² at the time of surgery. The absence of an A1 segment on the right may have influenced the extent of the lesion and probably accounts for its asymmetry.

The amnesia and behavioral changes that may occur after the repair of an ACoA aneurysm have been considered characteristic enough to constitute "the ACoA syndrome,"^{7,10} but have not previously been correlated with the underlying pathologic findings. In other patients described in the literature, mechanisms including vasospasm, hematoma formation, transtentorial herniation of the mesial temporal lobes, and hydrocephalus may have been responsible for the clinical deficits.⁹ Therefore, the clinical picture and underlying pathologic findings may not be identical in all cases of this type.

Neurologists recognize that a severe and relatively isolated anterograde memory deficit ("amnesic syndrome") is almost always due to bilateral limbic system dysfunction.³³ The lesion we have described, although small and discrete, involved several different nuclei each with extensive bilateral connections to many different areas of the brain. It is difficult to determine whether the observed clinical deficits resulted from loss of function of the infarcted structures themselves, or from interruption of links between other brain regions subserving memory. Similar problems mar interpretation of other human data: patient HM³⁴ has bilateral, extensive, surgically-induced mesial temporal lesions; patient NA³⁵ suffered penetrating brain trauma that must have resulted in damage to more than just the left mediodorsal thalamic nucleus³⁶; the lesion responsible for Korsakoff's psychosis is disputed,³⁷ and, in view of its metabolic cause, may not be fully demonstrable by routine histopathologic techniques.

Thus, while we have attempted to correlate this patient's amnesia with the underlying anatomical pathology, precise delineation of the minimal lesion producing this type of memory deficit must await further detailed clinicopathologic studies. However, available evidence suggests that the disruption of the interaction between the limbic system and cortical memory storage sites is critical for the production of the amnesic syndrome.^{38,39}

The Basal Forebrain

The basal forebrain region comprises the heterogeneous set of telencephalic structures on the medial and ventral aspects of the cerebral hemispheres.⁴⁰ There is no consensus regarding its exact boundaries but basal forebrain structures are generally taken to include the septal area,

olfactory tubercle, subcommissural region (substantia innominata), and parts of the amygdala.⁴⁰

The human septum comprises two major parts: a thin dorsal part, the septum pellucidum, made up of glial cells and fiber bundles; and a wider basal portion, the septum verum or true septum (here called the septum), which contains the nuclei.⁴¹ The terminology applied to this region has been a source of confusion and disagreement because of species differences and the lack of clear demarcation between cell groups and between gray matter and fiber pathways.⁴⁰ Andy and Stephan⁴¹ divided the septal nuclei into dorsal, ventral, medial (including the nucleus of the diagonal band of Broca [ndbB]), and caudal (including the bed nucleus of the stria terminalis) groups. Other authors^{42,43} divide them more simply into lateral and medial groups and maintain the separate identity of adjacent nuclei. The septal nuclei have connections with: the hippocampus through the precommissural fornix; the amygdala through the diagonal band and stria terminalis; the anterior perforated substance; and the midbrain reticular formation and hypothalamic nuclei through the medial forebrain bundle (MFB).^{43,44}

The MFB is thought to convey ascending influences from the brainstem reticular activating system, which are then relayed to the cortex for the modulation of cerebral arousal.^{45,46} This patient's septal lesion would have destroyed many connections of the MFB and may have contributed to his altered state of arousal.

Currently there is much interest in the basal forebrain region as the site of origin of a system of cholinergic neurons projecting to the entire cortical surface.⁴⁷ In the rat, there exists a highly somatotopically organized cholinergic septohippocampal projection,⁴⁸ which has a role in learning and memory.^{49,50} Mesulam et al⁴⁰ described four distinct groups of cholinergic neurons in the basal forebrain region of the rhesus monkey. The cell bodies within the medial septal nucleus, and some of those within the ndbB, provide the major cholinergic input of the hippocampus; others within the ndbB provide the major input into olfactory structures. The projections of the group located in the nucleus basalis of Meynert (nbM) of the substantia innominata are the most widespread and are directed to the amygdala and the cortical mantle of the hemispheres. An homologous system of

large cholinergic neurons is also present in the human brain.^{51,52} Most of these cells are found in the nbM but others are located in the medial septum, the ndbB, the ventral and lateral edges of the globus pallidus and the white matter below the putamen and nucleus accumbens⁵¹—areas which were destroyed by the lesion in this patient. They provide cholinergic input to the cortex but precise topographical details have not yet been elucidated.

The exact function of this basal forebrain magnocellular cholinergic system⁵¹ (BFMCS) are unknown. Preferential degeneration of this system, most marked in the nbM, occurs in Alzheimer's disease (AD),^{53,54} suggesting that the BFMCS has a role in higher cerebral functions. Mesulam et al⁴⁰ proposed that the particular pattern of cognitive deficits in any one patient with AD would reflect the distribution of cell loss in the BFMCS. They also suggested that the pathways from the ndbB and medial septal nuclei to the hippocampus may subserve memory and arousal functions. The findings in this patient provide support for these contentions. The septal nuclei, ndbB and adjacent areas were destroyed but the more caudal parts of the BFMCS, including the nbM, were spared. The patient suffered disturbances in arousal and was profoundly amnesic, but his intellect was otherwise preserved.

Nucleus Accumbens

The nucleus accumbens lies between the septal nuclei and the caudate-putamen. In its development and efferent connections it more closely resembles the latter,⁵⁵ but unlike the striatum, it receives its main cortical input not from the neocortex, but from the hippocampus.⁵⁶ Since (in the rat) it also receives input from the amygdala it has been termed, together with the ventral pallidum, the limbic striatum.⁵⁷ The ventral pallidum is the rostroventral portion of the external pallidal segment that extends into the basal forebrain beneath the anterior commissure.⁵⁶ Nauta and Domeick⁵⁶ have proposed that the limbic striatum represents "the interface between the respective neural mechanisms underlying the motivational and the more strictly motor aspects of movement." The association, in this patient, of apathy, loss of volition, and lack of spontaneity with lesions in the nuclei accumbens and rostroventral pallidal areas provides support for this concept.

The ventral pallidum also has con-

nections with the medial dorsal nucleus of the thalamus,⁵⁶ which, through clinicopathological correlation⁵⁸ and experimental observation,⁵⁹ is considered to be important in memory function. It is therefore possible that disruption of these connections also contributed to this patient's amnesia.

Neurochemical Aspects

The MFB and nucleus accumbens form part of the mesolimbic dopaminergic system.⁶⁰ That dopamine agonists may be effective therapy for the apathy observed in patients with the ACoA syndrome is suggested by the observation that lergotril and bromocriptine produced dramatic improvement in a patient who became akinetic and mute following surgical removal of a tumor from the anterior hypothalamus.⁴⁶ Catecholaminergic systems are also involved in memory, although their exact role is not clear.⁶¹ Clonidine enhances (but does not normalize) memory in patients with Korsakoff's psychosis,⁶² but, to our knowledge, has not been tested in patients with the ACoA syndrome.

Attempts to enhance function in the degenerating BFCMS of patients with AD by the administration of cholinomimetic agents have met with little success.⁶³ This may be a reflection of the difficulties of administering non-toxic, centrally acting cholinomimetic drugs to humans, or an indication that the cholinergic deficit is not function-

ally significant in patients with AD.⁶⁴ Support for the latter notion comes from a study in which rats given ibotenic acid lesions of the basal forebrain lost recent memory function, but then spontaneously regained it over a period of several weeks, despite persistent cholinergic deficiencies.⁶⁵ It remains to be seen whether cholinomimetic therapy improves memory in patients with the ACoA syndrome.

Several neuropeptides, including vasopressin, have been implicated as having a role in memory.⁶⁶ It is, therefore, of interest that chronic therapy with dDAVP nasal spray had no effect on our patient's neuropsychologic deficits.

Diabetes Insipidus

Disturbed salt and water metabolism posed major problems in the management of this patient, and was ultimately responsible for his demise.

Antidiuretic hormone is found in virtually all cells of the supraoptic nuclei and some of the cells of the paraventricular nuclei of the hypothalamus.⁶⁷ The fact that the supraoptic nuclei were spared by the lesion in this patient may well explain why his diabetes insipidus was "partial." It is more difficult to explain the isolated infarcts in the paraventricular gray, well separated from the main lesion. Crompton⁶⁸ described similar hypothalamic microinfarcts in 63 of 106

patients dying shortly after aneurysmal subarachnoid hemorrhage. They were most common with ACoA aneurysms and were often associated with cortical and basal ganglia infarcts, but they were no more frequent in patients treated surgically than in those managed conservatively. Vasospasm and distortion of the fine hypothalamic arteries produced by subarachnoid bleeding were considered possible pathogenetic factors.

Lesion studies and stimulation experiments in animals have shown that drinking behavior can be influenced by the hypothalamus and other limbic structures.⁶⁷ For example, septal lesions in the rat cause increased water uptake.⁶⁹ It is therefore not unreasonable to suppose that this patient's septal lesion could have contributed to the derangements in salt and water homeostasis by interfering with thirst mechanisms and drinking behavior. It is also possible that his amnesia led to poor compliance with the dDAVP therapy; the consequent fluctuations in the osmolarity of the internal milieu producing the episodes of diffuse cerebral dysfunction.

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