Selective traumatic infarction of the human anterior hypothalamus

Clinical anatomical correlation

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A case of assault with bilateral manual avulsion of the eyes was followed by highly selective infarction of the anterior hypothalamus. The hypothalamic infarction occurred as a result of avulsion of part of the optic chiasm together with the anterior perforating arteries passing through it. Following this assault, symptoms of hypothalamic dysfunction included altered thermoregulation, alternating diabetes insipidus, and inappropriate antidiuretic hormone (ADH) secretion, altered patterns of sleep and arousal, and changing cardiac arrhythmias. The case casts light upon the vascular supply of the human hypothalamus and on the degree of localization existing for various hypothalamic functions.

KEY WORDS: hypothalamus, optic chiasm, optic nerve, thermoregulation, traumatic avulsion of eyes, cardiac arrhythmia, inappropriate ADH secretion

The human hypothalamus is known to have a complex role involving specific neuroendocrine pathways to the anterior and posterior hypophysis, the regulation of autonomic functions, and the integration of these functions with certain behavioral patterns. Damage to this highly specialized center has been identified in a wide variety of pathological conditions.

In many cases of hypothalamic injury, the presence of lesions in related or distant structures precludes clear delineation of the symptomatology due to the hypothalamic lesion. In the case presented here, lesions topographically confined to the anterior hypothalamus permit definition of those symptoms that are the direct result of anterior hypothalamic destruction.

The correlation of hypothalamic lesions with endocrine disturbances is well known. There is, however, little information about non-endocrine disturbances of the human hypothalamus. Cardiovascular abnormalities such as occur in acute human traumatic and vascular conditions have recently been ascribed to the release of catecholamines associated to raised intracranial pressure (ICP) acting on the diencephalon.

We describe a case of acute vascular injury of the anterior hypothalamus that occurred without compromise of other cerebral functions apart from visual, and without raised ICP. The patient demonstrated changing cardiac arrhythmias, including severe atrial arrhythmias with ventricular escape rhythms, altered thermoregulation, altered patterns of sleep and arousal, and alternating phases of disturbed fluid balance, characterized by the initial development of diabetes insipidus followed by the syndrome of inappropriate antidiuretic hormone (ADH) secretion.

Case Report

This healthy 64-year-old woman was attacked by an acutely psychotic assailant, and suffered traumatic manual avulsion of both eyes.

On admission to hospital she was awake and able to answer simple questions and obey simple commands. However, she was disoriented to time, place, and situation, and unable to recall the assault or other recent events. The rest of the neurological examination was normal. Her blood pressure was 140/80 mm Hg, and the pulse was regular with a rate of 60/min. General physical examination, and chest and skull films were normal. During the following 5 hours and after surgical repair of the orbital lesions, her blood pressure dropped to 95/70 mm Hg, with a pulse rate of 46/min. Her skin temperature remained normal. Ten hours after the assault she began to develop episodes of sino-atrial arrest with appearance of junc-
FIG. 1. Base of the brain following its removal from the skull. Cut ends of carotid arteries are seen. Small penetrating arteries arise from the anterior segment of the posterior communicating artery and are associated with small recent hemorrhages in the region of the disrupted optic chiasm.

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General Pathological Findings

Significant abnormalities in the general autopsy were limited to the presence of acute bilateral bronchopneumonia.

The heart weighed 300 gm and was normal apart from a mild degree of left ventricular hypertrophy. Valvular disease and myocardial lesions were absent and mural thrombus was not present in any chamber. The coronary arteries were free of atheromatous occlusive lesions.

Gross Neuropathological Findings

The brain was removed by lifting the intact olfactory bulbs and tracts from the olfactory grooves and transecting the internal carotid arteries (ICA's) immediately before the origin of the posterior communicating arteries (PCoA's). The intact pituitary stalk was cut close to the infundibulum. It was unnecessary to transect optic nerves since these were both completely absent. The brain weighed 1290 gm.

Detailed examination of the small arteries in the region of the optic chiasm revealed small perforating branches arising from the supraclinoid ICA's, and the PCoA passing medially, posteriorly, and superiorly, to supply the optic tracts, the tuberal region, and the pituitary stalk. Other small arteries arising from the supraclinoid ICA and the PCoA ended in small areas of hemorrhage beneath or in the optic chiasm and infundibular area. Branches of the anterior cerebral and the anterior communicating arteries (ACoA) were obscured by the necrotic and hemorrhagic tissue of the optic chiasm. The lamina terminalis was infarcted, resulting in free communication between the third ven-

mOsm/kg prompted therapy with Pitressin (vasopressin).

On her fourth day in the Intensive Care Unit (ICU), the patient was restless. Her monitor showed sinus bradycardia with occasional VPB's and her temperature returned to normal. The electroencephalogram (EEG) showed the presence of diffuse low-voltage theta activity without focalization. She continued with the fluctuating response to commands and communication, and episodic restlessness during the next week.

By the end of her second week in ICU, the EKG returned to normal, but she again became hypothermic and hypotensive. She developed marked hyponatremia and low plasma osmolality characteristic of inappropriate ADH secretion. The EEG's repeatedly showed diffuse theta activity with the presence of delta waves over mid-frontal areas. Pulmonary and cerebral scintigrams were normal.

During the third and final week in hospital she developed hyperthermia and became progressively comatose. An infectious pulmonary picture preceded her death 20 days after the initial injury.

Autopsy Findings

The blood pressure returned to normal, but an irregular cardiac rate of 40/min persisted during the next few hours. Nonspecific ST-T changes and frequent ventricular premature beats (VPB) were noted without electrocardiographic (EKG) evidence of myocardial damage. Hypothermia developed 40 hours after the assault, and from this time on the patient was intermittently awake or drowsy. At times, she obeyed simple commands and at other times she did not. She sometimes refused to give verbal answers to questions. The neurological examination was normal.

Fifty hours after the assault, series of VPB's preceded bouts of paroxysmal atrial tachycardia admixed with junctional rhythms. Periods of sinus arrest lasted for 7 to 8 seconds. Abnormal electrolytes characteristic of diabetes insipidus, with a sodium of 178 mEq/liter and a plasma osmolality of 374

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tricle and the subarachnoid space. The mamillary bodies appeared normal (Fig. 1).

Examination of the base of the skull revealed absence of optic nerves, partial occlusion of the optic canal on the right side by blood clot, and no visible ophthalmic arteries (Fig. 2).

Anatomical Terminology of the Hypothalamus

Since no distinct anatomical boundaries exist between them, the nuclei of the human hypothalamus can be subdivided according to different landmarks. As a result of this, the hypothalamic nuclei have been grouped and classified in a variety of ways giving rise to discrepancies that affect comparative studies. With the exception of certain magnocellular nuclei, the majority of the small-cell nuclei are ill defined with neurons immersed in a plexiform matrix of fiber circuits. 18,25,29,57,64,66

For the purpose of a comparative topographical evaluation of the lesions involved in this case, two criteria were applied to analyze the serial coronal sections of the hypothalamus studied: 1) division into three rostrocaudal regions: preoptic-anterior, middle-tuberal, and posterior-mammillary; and 2) division into three longitudinal zones; periventricular, medial, and lateral.

Post-Fixation Neuropathologic Findings

A section through the preoptic recess (Fig. 3) revealed massive symmetrical necrosis of the entire preoptic hypothalamus, predominantly in the periventricular and medial zone, with effacement of the corresponding preoptic periventricular nucleus and medial preoptic nucleus. Compromise of the lateral zone was seen mainly on the right lateral preoptic

FIG. 3. Coronal section of the base of the brain at the preoptic level, showing infarct (delineated by dots). H & E-LFB.
nucleus. Superiorly, this latter lesion extended into the
area of the right nucleus accumbens septi, and merged
bilaterally into the fasciculi diagonalis of Broca. The
anterior perforate areas were preserved. The anterior
optic chiasm was totally necrotic and distorted and
was the site of a large intrachiasmal hemorrhage.

Caudal to the region just described, a section was
made at the level of the anterior commissure (Fig. 4).
This section revealed symmetrical necrotic involve-
ment of the tuberal hypothalamus, compromising the
three zones and their nuclei: paraventricular and in-
fundibular, dorsomedial and ventromedial, and supra-
optic, respectively. The lateral hypothalamic nuclei
were partially affected and were bounded by normal
substantiae innominata regions. The median portion
of the anterior commissure was involved in a roughly
symmetrically delineated fashion. The optic tracts
were subtotally involved, with the exception of their
superolateral margins.

More caudally, a section corresponding to the
mammillary nuclei showed good preservation of the
normal structure (Fig. 5). A small area of edema of
the more lateral portion of each medial mammillary
nucleus was seen, mainly on the left side.

Microscopic sections of the involved hypothalamic
areas showed infarction 2 to 3 weeks old, character-
ized by necrotic nerve cells, gliovascular prolifera-
tion, and macrophages admixed with numerous
perivascular hemorrhages. The magnocellular nuclei
showed the more prominent microhemorrhagic
lesions. Reactive gliosis and axonal swellings were
more evident in the marginal fields.

The optic chiasm showed necrosis with prominent
axonal degeneration and large numbers of macro-
phages (pigment- and lipid-laden). The looseness of its
structure contrasted in some areas with the dissecting
hemorrhages seen macroscopically. The optic tracts
showed similar infarcted features that tapered off
posteriorly at the level of the mammillary nuclei,
where only a slight degree of edema was present. The
medial mammillary nuclei showed only loose texture
resulting from mild edema. The adeno- and neuro-
hypophysis were normal. The pituitary stalk showed
numerous axonal swellings near the upper end of the
stalk, but there was no evidence of necrosis.

Sections of the optic canals showed absence of optic
nerves and presence of necrotic, hemorrhagic tissue.
Sections of midbrain showed minimal chromatolytic
changes in the oculomotor nuclei.

Discussion

Pathogenesis of Hypothalamic Lesions

The effect that avulsion of the eyes and optic nerves
produces on the hypothalamus is not clear since
published scientific reports of unilateral and bilateral
enucleation, mostly self-inflicted by psychotic
patients, deal chiefly with the psychiatric and ophtalm-
omological aspects of the cases. The patient, reviewed by Goodhart and Savitsky, and
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originally reported by Goffin in 1887, apparently developed progressive dementia after the episode; the brief description of this case did not allude to clinical hypothalamic symptomatology. In none of the 30 reported cases was any reference made to specific hypothalamic disturbances. This is surprising, in view of the fact that in a number of these cases the length of the torn optic nerve reached 4.5 cm and apparently included anterior chiasm tissue.

**Mechanical Factors.** The region between the optic nerve and the chiasm is mechanically the weakest point between the globe of the eye and the anterior opticohypothalamic pathways. The optic nerve segments in the orbit and in the optic canal are supported both by dura mater and by an internal skeleton of collagenous trabeculae, and these trabeculae continue posteriorly to the optic chiasm. All such mechanical support is lost in the chiasm itself. This was confirmed experimentally by Coppez in 1929.

In several cases of unilateral enucleation, the only neurological damage described was temporal hemianopsia of the preserved contralateral eye.

**Vascular Factors.** The chiasmatic region exhibits considerable variation in its relationship to the surrounding vascular and meningeal structures. The disruption of penetrating arteries in our case points to a vascular mechanism for the production of the hypothalamic lesion.

To understand the pathogenetic mechanisms involved in the hypothalamic injury, it is necessary to emphasize certain particularities of the anterior and tuberal hypothalamus vascularization. The arterial supply to this region is provided by a rich confluence of small perforating branches arising from the proximal anterior cerebral (PACA), ACoA, supraclinoid internal carotid (SICA), PCoA, and posterior cerebral arteries. These perforating arteries first irrigate the optic structures and the pituitary stalk and, passing upward through these structures, reach their final territory in the hypothalamus.

The blood supply of the preoptic-anterior hypothalamus, septal region, and median anterior commissure is supplied partly by the PACA, which gives rise to a significant number of fine branches that penetrate the brain through the optic tracts and anterior perforated substance, and partly by fine branches originating from the ACoA that penetrate through the optic chiasm and the lamina terminalis. The tuberal area is supplied partly by the "circuminfundibular anastomosis" or "inferior group of vessels," which consists of the convergence of arteries arising from the SICA, PCoA, and PCA, giving the major supply to the optic chiasm and pituitary stalk and partly by the premammillary arteries or artery that arise(s) from the anterior half of the PCoA and terminate(s) in the anterior third of the optic tracts, the premammillary area and posterior part of the optic chiasm.

The main venous drainage of the anterior and tuberal hypothalamus is shared also by the optic struc-
tutes, draining toward the anterior communicating vein, the anterior cerebral veins, the retrochiasmatic venous arch, and the tuberous veins that finally end in the basilar vein. \[37, 60\] Superior parts of the anterior hypothalamus (fornical) drain toward tributaries of the internal cerebral vein. \[52\]

In our case, an unusual traction force was applied to the optic nerves that resulted in side-to-side and forward displacement or shearing of the optic chiasm and optic tracts with final anterior detachment of the optic nerves. During this process, direct stretching with subsequent spasm and direct shearing with rupture affected simultaneously and selectively the perforating arterial branches as well as the fine draining veins, all of which are closely attached to the chiasm and optic tracts and resulted in the infarction of the anterior hypothalamus.

**Destructive Lesions Confined to the Hypothalamus**

Neuropathological descriptions of acute vascular damage limited to the hypothalamus are few in the literature. Lesions produced by primary ischemic vascular disease have only been reported in clinical descriptions that ascribed certain specific symptomatology to occlusive circulatory lesions of the anterior hypothalamus. \[25, 81, 107\]

The vast majority of vascular lesions described in the literature were found after closed cerebral trauma. \[11, 28, 30, 101, 102\] Focal “micro-hemorrhages” (perivascular-parenchymal) disrupt the periventricular nuclei, especially the para-tuberarcal nucleus, the medial nuclei, the supraopti nucleari (lateral hypothalamus), and the mammillary bodies. The infundibular region often suffers infarction, usually of the tuber-stalk junction. Shearing forces induced over the relatively fixed pituitary stalk and optic nerves by the movement of the hypothalamus would damage the stalk vessels and supraoptic nuclei, respectively. Infarction was also described in the mammillary bodies. Similar types of lesions (micro-hemorrhage, infarction) were found by Crompton \[25\] in his previous study of 65 cases of subarachnoid hemorrhage with associated lesions of the hypothalamus. He demonstrated a significant preponderance of the ischemic lesions (47 out of 65 cases) in the anterior-preoptic region, also reported by Smith. \[86\] In the majority of published cases, lesions were present not only in the hypothalamus but in the pituitary gland, \[86\] and other parts of the brain as well. This was true of almost all of Treip’s cases \[101, 102\] and in 88% of Crompton’s cases. \[25, 34\] Therefore, it is difficult to describe the specific symptomatology resulting from the damage of the hypothalamus, considering the concurrently raised ICP produced by edema or intracranial hemorrhage.

**Effects of Hypothalamic Lesions**

**Cardiac Arrhythmias.** Electrocardiographic (EKG) changes consisting of a variety of atrial and ventricular arrhythmias, abnormalities of the QRS, T-wave, and S-T segment have been described in intracranial pathology, predominantly in subarachnoid hemorrhage, ischemic and hemorrhagic strokes, head trauma, meningitis, and brain tumors. \[1, 17, 27, 35, 40, 41, 55, 70, 74, 79, 82, 91\] Several sympathovagal-imbalance mechanisms have been postulated as responsible for these EKG changes. They are as follows: 1) hypothalamic lesion/stimulation; \[9, 35, 73\] 2) fronto-orbital cortical lesions/stimulation; \[24\] 3) raised ICP; \[40, 57, 97\] and 4) traction (surgical) of cerebral arteries. \[86\]

Few reports deal with focal stimulation/destruction of the human hypothalamus and autonomic dysfunction. Sano, et. al., \[83\] described hypertension, tachycardia, and mydriasis by stimulation of the posteromedial hypothalamus. Results of operative destruction were described as “a tendency to a decrease in sympathicotonia or an increase in parasympathicotonia.” \[119, 83\]

Necrosis of the anterior fornix and infundibulum resulted in persistent bradycardia in one case reported by Treip. \[102\] Bilateral diffuse ischemic lesions and perivascular hemorrhages predominantly in the periventricular zone have been seen associated with myocardial and EKG changes in cases of subarachnoid hemorrhage. \[35\]

Many experimental studies in animals have been performed in attempts to show a pathogenetic role for the hypothalamus in the onset of cardiac arrhythmias and extrapolate the results to human arrhythmias observed in lesions of the central nervous system. In 1930, Beattie clearly evoked cardiac arrhythmias by stimulation of the posterior hypothalamus, and first set a differentiation between two areas, anterior and posterior of the hypothalamus. \[40, 71\] A full gamut of ventricular and atrial arrhythmias has been consistently evoked with a great variety of accompanying pressor or depressor effects. \[80, 95\]

Traditionally, vagal responses were related to stimulations of the anterior and medial regions, and sympathetic or cardio-accelerator responses were obtained from posterolateral areas. \[84, 106\] These responses were abolished by cervical spine transection. However, these data are controversial, subjected to a large number of experimental variables and uncertainty on the localization of centers. \[46, 57, 69, 71, 73\]

Various hypothalamic neuronal pools and pathways overlap significantly, and it is possible that areas regulating cardiac rhythm, blood pressure, and body temperature may be affected either primarily or secondarily giving contradictory results. \[37, 80\] Electrical stimulation may excite structures non-selectively, locally and at a distance, and the responses also vary with intensity of current. \[9, 108\]

Also, specific “defense reaction” mechanisms have to be considered. That is, the adaptive responses by means of which depressor mechanisms suppress concomitant pressor responses. \[14, 108\] Recently, there has

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been cumulative evidence demonstrating the primary mediation of mesencephalic-hypothalamic loop inhibitory mechanisms in the regulation of heart rate.53,86 The normal homeostatic functions are integrated at a medullary level of baroreceptors. Hypothalamic baroreceptor afferents appear to have inhibitory connections that alter the feedback sensitivity of those medullary receptors.

Refined electrophysiological studies of unit activity have allowed the identification of single interneuron populations and circuits with vasopressor and vasodepressor activity in both anterior and posterior hypothalamus. Input from atrial and carotid baroreceptor and chemoreceptors have been registered in interneurons of the anterior (medial and lateral) zone.53 Our case conclusively demonstrates the disruption of these circuits with the uncontrolled triggering of vagal sino-depressor activity which allowed the secondary ectopic rhythms. In the absence of cardiac lesions, this abnormal response reverted after new compensatory mechanisms were established and the sinus activity returned to normal.

Thermoregulatory Disturbances. Early in the investigation of the cardiovascular control mechanisms, lesion-stimulation studies led to the conclusion that there were two separate hypothalamic regions for the regulation of heat loss and heat conservation. These regions were, respectively, the preoptic-anterior and preoptic-posterior areas.67,88 However, subsequent experimental studies showed that when the temperature of the preoptic-anterior region was altered, warming and cooling was obtained, suggesting that this center contained mechanisms for both heat production (shivering) and heat dissipation (vasodilatation-hemorrhage, and cerebral trauma).8

Pathological mosensitive neurons in lower animals demonstrated body temperature in relation to the changes of the environment.8,93,106 These findings explained why experimental studies showed that when the temperature regions were, respectively, the preoptic-anterior and posterior hypothalamus, input from atrial and carotid baroreceptor and chemoreceptors have been registered in interneurons of the anterior (medial and lateral) zone.53 Our case conclusively demonstrates the disruption of these circuits with the uncontrolled triggering of vagal sino-depressor activity which allowed the secondary ectopic rhythms. In the absence of cardiac lesions, this abnormal response reverted after new compensatory mechanisms were established and the sinus activity returned to normal.

Numerous experimental observations point toward diabetes insipidus (DI) as the result of hypothalamic lesions (for instance, in the median eminence, or pituitary stalk).62,75,76,86,96 This rare condition has been reported in an extensive variety of human hypothalamo-hypophyseal lesions, including closed-head trauma, ischemia, hemorrhage, inflammation, and surgical manipulation. Lesions can directly affect the above-mentioned nuclei or, more frequently, disrupt the unmyelinated axons of the supra-opticohypophysial tract.6,30,75,87,94

Transient, permanent, and recurrent forms of DI have been described. Association with the inappropriate ADH syndrome has also been noticed, presumably due to delayed release of the hormone from injured tissue.38,77 The inappropriate ADH syndrome has also been associated with a variety of destructive lesions of the hypothalamo-neurohypophyseal axis, but the actual pathophysiological mechanisms are unknown.6,19,38,50

Our patient clearly developed DI 72 hours after the vasculotraumatic lesion to the hypothalamus; DI lasted for 6 days, at which time plasma osmolality values returned to normal. The inappropriate ADH syndrome that developed 48 hours later and persisted until her death cannot, however, be clearly distinguished from the other concurrent factors, such as hypovolemia, and sustained hypotension. The pathological findings consistent with partial damage to the infundibular neurovascular zone are in keeping with the transient DI presented by the patient.

Sleep and Arousal Mechanisms. Lesions of the preoptic-anterior hypothalamus have not resulted in hypersonnia or an established comatose state.15 Although there are no proven specific “sleep nuclei” in the anterior hypothalamus,61 experimental lesional studies in lower animals resulted in reduced drowsiness, and this region is considered the center for integrated sleep induction and heat loss in hibernating animals.90,99,100

Contrary to these findings, lesions placed in the posterior hypothalamus interrupt mesencephalic-thalamo-cortical pathways (reticular activating system), and cause hypersonnia and deep coma in animals and in humans.32,78,86

The disturbance in the sleep-wake cycle of our case (alternating diurnal periods of insomnia and drowsiness) is of interest because of the absence of lesions.
of the posterior hypothalamus or raised ICP to explain drowsiness.

**Conclusion**

The mechanism of hypothalamic injury secondary to bilateral traumatic avulsion of the eyes must include reference to both mechanical and vascular factors. Selective destruction of the anterior hypothalamus (and of neighboring structures of fornices and anterior commissure) has not previously been carefully studied in the human. The case reported here permits us to attribute alteration of cardiac rhythm, loss of thermoregulation, abnormal fluid homeostasis (DI and inappropriate ADH syndrome), and altered sleep-arousal patterns to selective destruction of the anterior-hypothalamus. Disorientation and loss of recent memory may possibly result from interruption of the fornices anterior to the mammillary bodies. These findings are significant since surgical entry of the chiasmatic area may result in anterior hypothalamic syndromes if small penetrating arteries are not carefully preserved.

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