Hypothalamic Hamartoma in a Dog

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Abstract. A 10-month-old female, Wire-haired Pointing Griffon dog had a hamartoma of the hypothalamus. Episodes of sudden flaccid collapse had increased in frequency and duration for 7 months. Cerebrospinal fluid pressure was normal. A flat, pedunculated mass, 2.5x3.0x0.9 cm, covered the brain stem between the pituitary gland and pons. Its 1.2-cm-diameter connection to the hypothalamus obliterated the mammillary bodies and extended to the tuber cinereum, distorting the hypothalamus and displacing the third ventricle which also divided the rostral part of the mass. The tissue of the hamartoma resembled gray matter with bullous cytoplasmic vacuolation of many neurons, spongiform change, gc-mistocytosis and microscopic foci of calcification.

Since a hamartoma of the hypothalamus in man was first described in 1935 [6], more than 30 cases have been reported [5, 8, 10, 12, 13]. This rare malformation, up to several centimeters in diameter and composed of redundant gray matter projecting from the base of the brain, arises usually from the tuber cinereum caudal to the hypophyseal stalk and also arises within the mammillary bodies [12]. The condition is classically associated with precocious puberty and usually occurs in males [10].

There is little documentation of hamartomas of the central nervous system in animals. A hamartoma of the mammillary bodies seen during necropsy of a 7-month-old male Boxer dog with distemper encephalitis had not produced clinical dysfunction [7].

This paper reports what appears to be the first case of a hypothalamic hamartoma causing neurologic disease in an animal.

Case Report

A female Wire-haired Pointing Griffon dog was bought when she was 3 months old. She had neurologic episodes which, during the next 7 months, gradually increased in frequency from fortnightly to two or more times a week. They progressed from several 1-min episodes of ataxia and disorientation to more severe episodes of sudden flaccid collapse and apparent unconsciousness, lasting up to several minutes. Recovery was rapid after these cataplectic-like attacks which sometimes occurred while the animal was eating. On the day of admission, three such attacks were seen at 30-min intervals. The 26-kg dog was shy, had no history of precocious sexual development, and had not been in estrus.

Results

Clinical Findings

Complete blood count, blood urea nitrogen and glucose, and serum alanine
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Fig. 1: Hypothalamic hamartoma (arrows).

Aminotransferase, alkaline phosphatase and ammonia nitrogen values were normal. Bromsulphalein retention was increased to II % at 30 min (normally less than 5 %). The cerebrospinal fluid pressure, leukocyte count, and total protein were within normal limits. Urinalysis results were normal.

During a 9-day period of observation, the dog was alert and usually lay quietly in her cage. She had a tendency to circle to the left.

After provisional diagnosis of narcolepsy [2] and intramuscular injection with 40 mg of methamphetamine hydrochloride (Methedrine", Burroughs Wellcome and Co., Tuckahoe, N.Y.), she became hyperactive and circled to the left for 2 h before collapsing. She had tachycardia and hyperpnea, salivated excessively and remained recumbent but alert for 2 h. She then became progressively less responsive and died 2V: h later.

Gross Findings

At necropsy, there were extensive ecchymoses on the epicardial surface extending into the myocardium, and diffuse subendocardial hemorrhage in the left ventricle. The congested lungs contained several circumscribed foci of hemorrhage, about 1 cm in diameter, and there was atelectasis of the ventral borders of the diaphragmatic lobes. The liver was congested.

The pituitary gland nestled into the rostral border of an asymmetric, pedunculated mass that resembled normal cerebral tissue (fig. 1.2). The mass was attached to the hypothalamus and covered the ventral surface of the brain stem to the pons. Arising from the tuber cinereum lateral and caudal to the infundibulum on the left
and right sides respectively, the rostral part of the mass and its attachment were divided by the third ventricle (fig. 3). Most of the 1.2-cm-diameter connection with the caudal hypothalamus, however, was undivided and obliterated the mammillary bodies, distorting the hypothalamus and displacing the third ventricle (fig. 4). The caudal, free edge of the mass reached a maximum width of 3 cm, was mainly on the left side, and had a dorsoventral thickness of about 0.9 cm (fig. 5). Blood vessels were prominent within the leptomeninges covering the mass except in two flattened white areas on the right side and caudal edge of its ventral surface (fig. 2). The middle fossa of the cranial cavity was distended ventral to the mass.

Histologic Findings

Tissue specimens were fixed in 10% buffered formalin, embedded in paraffin, sectioned at 6 μm and stained with hematoxylin and eosin (HE). Sections of the hypothalamic mass and selected brain sections were also stained with periodic acid-Schiff (PAS), Holmes' luxol fast blue-periodic acid-Schiff, phosphotungstic acid-hematoxylin, Giemsa, Gomori's trichrome, and by Von Kossa's technique for calcium.

There was congestion of lung, liver and kidney. The myocardium and lungs contained many areas of microscopic hemorrhage in addition to those more extensive hemorrhagic areas seen grossly.

The hypothalamic mass had many neurons and glial cells irregularly distributed throughout the well-vascularized neuropil of mainly myelinated fibers, and resembled gray matter (fig. 6). Neurons varied in size, and the larger ones were often in...
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Fig. 3: Transverse section of brain caudal to the pituitary gland. Division of rostral pole of hamartoma (11) by third ventricle.

groups. A horizontal zone through the center of the mass had fewer neurons, more glial cells, and some linear orientation of myelinated fibers. The leptomeningeal covering contained bands of collagen and medium-sized blood vessels that penetrated the mass, often obliquely, to further demarcate a 1-mm-wide circumferential zone containing fewer neurons. This zone, in the white areas seen grossly on the ventral surface of the mass, was characterized by marked proliferation of small vessels, although its flattened leptomeningeal surface was free of large vessels and sharply bounded by an indistinct pia-arachnoid. Fewer neurons were scattered through the mass's hypothalamic attachment, which was mainly composed of bands of myelinated fibers.

Apart from generalized congestion, changes within the central nervous system were restricted to the mass and its connection to the hypothalamus. Most prominent was the distinctive bullous cytoplasmic vacuolation of many neurons (fig. 6, 7). Neurons of all sizes were affected, but this change was most severe in larger ones, where one or more cytoplasmic vacuoles greatly distended the cell body and displaced the nucleus and Nissl substance to the periphery. A large hyperchromatic nucleolus characterized the nuclei of some vacuolated neurons. There was no evidence of edema within the adjacent neuropil or around vessels. Occasionally a PAS-positive inclusion was seen within a small neuronal vacuole. There were areas of spongiform change within the neuropil consisting of vacuoles 20-50 \( \mu \text{m} \) in diameter, possibly representing the final stage of bullous neuronal vacuolation. Gemistocytic astrocytes frequently were seen, both singly and in small groups (fig.
Fig. 4: Caudal to section in figure 3. Displacement of third ventricle (arrow) and distortion of hypothalamus by its 1.2-cm-wide connection to the hamartoma (I-I).

7). Areas of calcification within the mass ranged from 10-μm-wide foci (possibly corresponding to former cell bodies), to a few areas of diffuse mineralization up to 200 μm wide.

Despite the macroscopic distortion of the hypothalamus and enlargement of the tuber cinereum, these structures had none of the microscopic degenerative changes seen in the mass and its attachment.

A diagnosis of hypothalamic hamartoma was made. Death was caused by acute methamphetamine poisoning, which produced pulmonary and myocardial hemorrhage.

Discussion

Hypothalamic hamartomas are characterized by their typical location and similarity of histologic structure, and comprise a specific entity amongst congenital malformations of the brain [13]. Their various-sized neurons, haphazardly assembled with neuroglial cells and bundles of nerve fibers, resemble adjacent hypothalamic cells [10]. It has been suggested [12] that these hamartomas result from displacement of tissue from this area of the embryonal neural tube after its temporary fusion with, and subsequent separation from, the rostral tip of the chorda dorsalis and prechordal plate.

Precocious puberty, the most striking and frequent sign in man, has been associated with a variety of human hypothalamic lesions and appears to reflect the location rather than the type of change [10, 13]. Despite marked distortion of the
hypothalamus in this dog, emphasized by the displacement of the thrid ventricle (fig. 4, 5), there was no evidence of endocrine dysfunction such as precocious puberty. Cataplexy-like spells are associated with idiopathic narcolepsy in man and the dog [21, but may be caused by organic disorders that involve the hypothalamus [31. as did the present mass.

While focal mineralization, spongiform change and astrocytic reaction within the mass were of longer standing, the bullous neuronal vacuolation could be attributed to the terminal episode of acute methamphetamine poisoning. It is more likely, however, that all these changes, restricted to the hamartoma and its attachment, were present before treatment. Strikingly similar neuronal vacuolation has been seen in human hypothalamic hamartomas [11, 13]. One of these also had large spongiform cavities and reactive astrocytes [11 as did the dog in my report; the other hamartoma had many corpora amylacea [113]. Such changes may reflect periodic compromise of circulation within these hamartomas. Despite reports of cerebral vascular changes with hemorrhage in acute amphetamine toxicosis [4, 111, recent experiments with rats and Rhesus monkeys have failed to produce central nervous system lesions, whereas myocardial hemorrhage was inconsistently seen in those animals that occasionally died within hours of a single intravenous dose (more than 1.5 mg/kg) of methamphetamine [9].

There was no evidence of hepatic disease to explain the increased bromsulphalein retention. Normal cerebrospinal fluid drainage and pressure apparently were
Fig. 6: Irregularly distributed neurons of various sizes, and glial cells within the hamartoma. Neuronal vacuolation. HE.

Fig. 7: Numerous gemistocytic astrocytes (arrows) and bullous vacuolation of a large neuron. HE.
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maintained by distention of the middle fossa of the developing cranial cavity to accommodate the hamartoma.

Acknowledgement

The author thanks Dr. J. G. Cunningham, Department of Small Animal Surgery and Medicine, Michigan State University, for clinical information.

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