

Different Electroclinical Manifestations of the Epilepsy Associated with Hamartomas Connecting to the Middle or Posterior Hypothalamus

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Summary: *Purpose:* The epilepsy associated with hypothalamic hamartomas (HHs) has typical clinical, electrophysiologic, and behavioral manifestations refractory to drug therapy and with unfavorable evolution. It is well known that only sessile lesions produce epilepsy, but no correlation has been established between the different types of sessile hamartomas and the diverse manifestations of the epilepsy. We correlate anatomic details of the hamartoma and the clinical and neurophysiologic manifestations of the associated epilepsy.

Methods: HHs of seven patients with epilepsy (ages 2–25 years) were classified as to lateralization and connection to the anteroposterior axis of the hypothalamus by using high-resolution brain magnetic resonance imaging. We correlated the anatomic classification with the clinical and neurophysiologic manifestations of the epilepsy as evaluated in long-term (24 h) video-EEG recordings.

Results: HHs ranged in size from 0.4 to 2.6 cc, with complete lateralization in six of seven patients. Ictal manifestations showed good correlation with the lobar involvement of ictal/interictal EEGs. These manifestations suggest the existence of two types of cortical involvement, one associated with the temporal lobe, produced by hamartomas connected to the posterior hypothalamus (mamillary bodies), and the other associated with the frontal lobe, seen in lesions connecting to the middle hypothalamus.

Conclusions: A consistent clinical and neurophysiologic pattern of either temporal or frontal lobe cortical secondary involvement was found in the patients of our series. It depends on whether the hamartoma connects to the mamillary bodies (temporal lobe cases) or whether it connects to the medial hypothalamus (frontal lobe cases). **Key Words:** Hypothalamic hamartoma—Epilepsy.

The hypothalamus is an area of the human brain located in the base of the diencephalon, very seldom involved in seizure activity. The most common pathology leading to epileptic foci in this region is the hypothalamic hamartoma (HH), a lesion intrinsically epileptogenic (1) that contains normal neurons and glial cells in an anarchic tissue organization.

The HH can have a pedunculated stalk or a sessile one. Although the latter is associated with epilepsy, the former is associated only with precocious puberty (2). This observation suggests that the epileptiform activity generated inside the hamartoma leads to clinical manifestations only when a sessile attachment to the hypothalamus allows its propagation to the diencephalon (3).

Several series of patients with this type of epilepsy (4–6) displayed diverse clinical and neurophysiologic

manifestations, along with a large variability in the macroscopic characteristics of the lesion (7,8). No study, however, has established a clear correlation between the detailed anatomic characteristics of the hamartomas and the clinical manifestations of the associated epilepsy.

In this study, we characterized a series of patients with epilepsy and HHs, from a clinical, neurophysiologic, and anatomic point of view and tried to interpret the results with the present knowledge of the organization of the hypothalamic–cortical pathways.

METHODS AND SUBJECTS

Methods

The patient population consisted of seven cases with epilepsy and HHs that were evaluated at the clinical neurophysiology laboratory of our institution. All had refractory focal epilepsy and were being considered for epilepsy surgery.

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The diagnosis of the hamartoma was based on magnetic resonance imaging (MRI) of the brain, showing a T₁ signal similar to that of the cortex and an increased signal strength in T₂ sequences that did not change in repeated MRIs. In one case, the diagnosis was confirmed by a stereotaxic biopsy.

To improve the anatomic characterization of the lesion, high-resolution volumetric T₁ images were obtained of the whole brain, allowing visualization in perpendicular planes, to better characterize the connection of the hamartoma to the hypothalamus.

All patients but one were submitted to long-term (24 h) continuous video-EEG, with 27 to 32 scalp electrodes, and multiple seizures were recorded. In one patient (case 4), only a 3 h interictal EEG could be recorded.

The hamartoma connection to the middle and posterior segments of the hypothalamus (Figs. 1 and 2) was determined. Involvement of the mamillary bodies was accepted when there was an interruption on the halo of hypersignal in T₁ surrounding these structures, in contact with the hamartoma mass. This criterion was important because in some cases, a significant shift and deformation was apparent, but the structure of the mamillary bodies did not change.

The ictal clinical and neurophysiologic data also were determined and tabulated along with the interictal EEG features (Table 2). When spikes had a maximum over two of the F_{7/8}, F_{3/4}, or Fp_{1/2} electrodes, the focus was considered frontal, whereas a maximum over two of the T_{5/6}, T_{3/4}, or F_{7/8} was taken as a temporal focus.

We then investigated the correlation between the ictal-interictal EEG features, the seizure characteristics, and the anatomic details of the connection to the hypothalamus.

Subjects

Case 1

A 9-year-old boy is the son of healthy and nonconsanguineous parents. Gestation and delivery were normal, and the motor and cognitive milestones were reached at the appropriate ages in the early years.

In the first year, brief (<1 min) laughing episodes were present in wakefulness and sleep, without the appropriate emotional context. These spells occurred on a daily basis, but after the first year they became rare.

At age 5 years, a hyperkinetic behavior was apparent, with severe difficulties of concentration on a single task and frequent episodes of aggression to other children. At this time, an increase was observed in the frequency of gelastic seizures that occurred daily. Tonic seizures with rotation of the head and eyes, elevation of the arm, as well as left clonic jerking of the eyelids and corner of the mouth occurred mainly at night, 2–3 times per week. The aggressive behavior became more severe as well as the learning problems at school. Motor seizures increased to

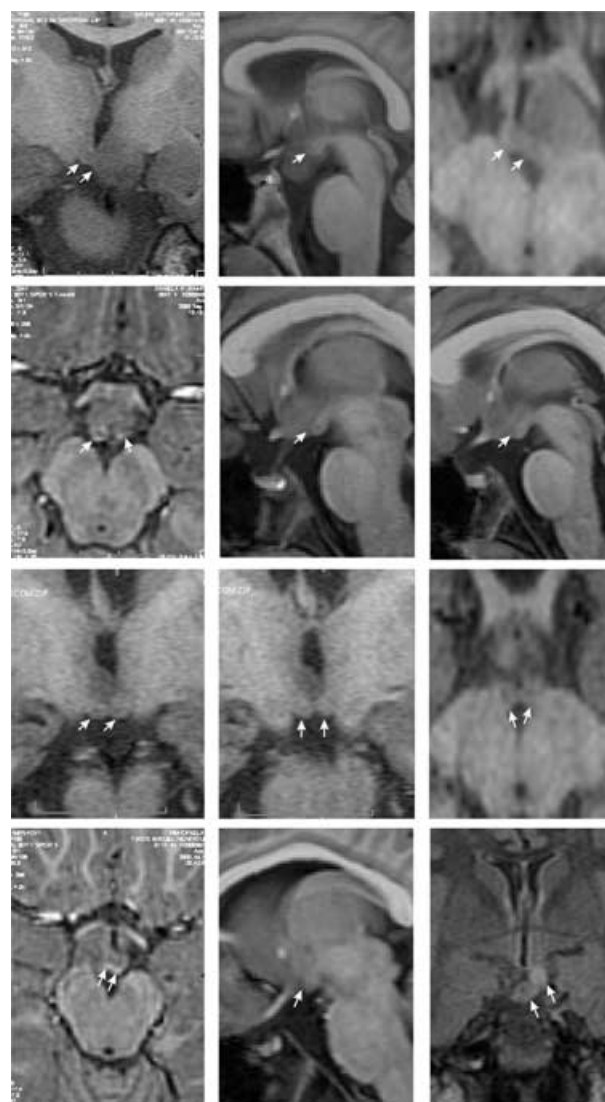


FIG. 1. Details of the anatomic connections of the hamartomas to the hypothalamus in cases sparing the mamillary bodies. Each row represents a spoiled gradient echo (SPGR) T₁ sequence of a different patient (cases 3, 6, 1 and 5, from above). The mamillary bodies are surrounded by a ring of increased signal (arrows), which, when present in perpendicular planes, is taken to mean that the hamartoma is not connected to this structure. Note that despite the significant shifts of the normal anatomic position in some cases, the structure of the mamillary bodies is preserved in all cases.

a daily frequency, and when occurring during the day, they produced a consistent fall to the ground at the end of the seizure. They lasted <1 min and were followed by a brief confusional period.

A brain MRI demonstrated a small HH, and a 24 h video-EEG documented bifrontal interictal spike activity as well as several gelastic seizures followed by tonic posture of the four limbs and upward deviation of the eyes, lasting <30 s.

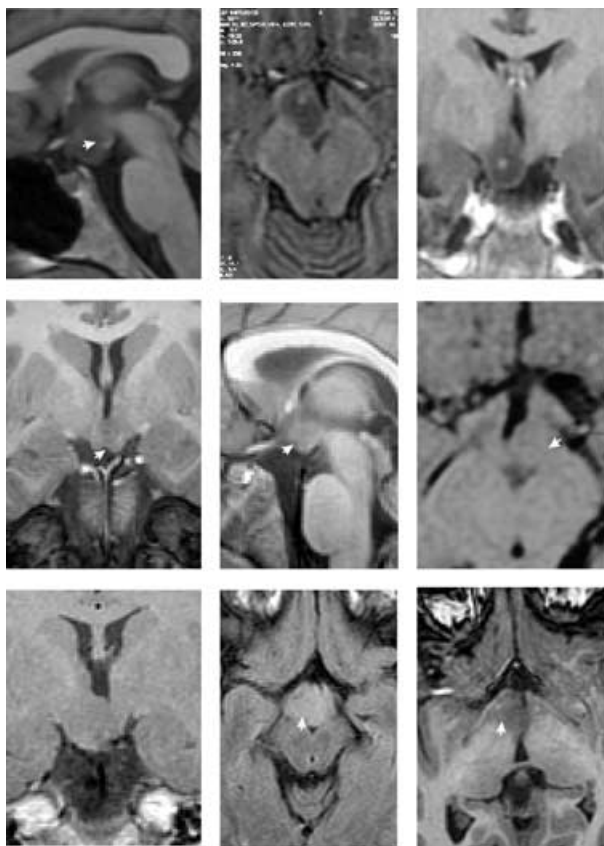


FIG. 2. Details of the hamartomas with connection to the mammillary bodies. As in Fig. 1, each patient is represented in a row (cases 4, 2, and 7, from above). An interruption of the ring of increased signal occurs in T₁ (arrows) in touch with the hamartoma mass, and this is taken as the point of connection.

Case 2

A 6-year-old boy is the second son of healthy and non-consanguineous parents. No problems were detected during gestation or delivery.

Motor development was normal until age 3 years, but language acquisition showed a slight delay. At this age, he started brief gelastic seizures, occurring several times daily and often associated with tonic turning of the eyes to the left and interruption of consciousness. Seizures also were noted during the night and proved resistant to pharmacologic therapy.

After onset of seizures, progressive behavioral disturbances, with hyperactivity, marked aggressiveness, and slowing of cognitive development became a major problem. The previous manifestations produced a major handicap in social interactions with children of the same age and even with the family members.

The EEG demonstrated temporal lobe spike activity, and the HH was seen in a brain MRI. A long-term video-EEG study demonstrated several gelastic seizures with no clear spike activity present in the scalp EEG.

Case 3

A 9-year-old boy is the son of healthy and nonconsanguineous parents. Gestation and delivery were uneventful and medically assisted. Motor and cognitive development was normal.

From the early months of life, gelastic seizures lasting seconds became apparent several times daily. No interruption of contact was present during these episodes. Between ages 2 and 3 years, several seizures produced rotation of the head and a drop to a seated position.

When he started school at age 6 years, severe learning problems became evident, and also a major difficulty in social interaction with children of the same age. At this age, drop attacks with turning of the head were present and occurred in isolation or more often after a gelastic seizure.

An EEG showed spike activity over the frontal lobes, and a head MRI evidenced the HH. A long-term video-EEG study demonstrated several postural seizures of the four limbs, with features suggesting supplementary motor area involvement.

Cases 4 to 7

Clinical data details were previously published (3) and are included in Table 1.

RESULTS

In six of seven patients, the hamartoma connected either to the left or right hypothalamus (Table 2). The volume of the lesion ranged from 0.4 to 2.6 cc, but all lesions had a sessile attachment to the middle or posterior hypothalamus. In three patients, the hypothalamic connection was established only in the middle area, whereas in two others, only a connection to the posterior areas (mammillary bodies) was seen (Table 2).

The interictal EEG revealed a consistent lobar involvement in each patient, which could be either temporal (three of seven) and/or frontal (five of seven). Patients 1 and 3 represent examples of frontal lobe secondary involvement, whereas patient 2 is an example of a temporal lobe case. Only one case showed simultaneous involvement of frontal and temporal lobes. Frontal spikes were usually present on both hemispheres, but the temporal spikes remained lateralized to the side of implantation of the hamartoma (three of three).

Several ictal events were recorded in six of seven patients, and these showed different combinations of gelastic seizures, gelastic seizures followed by cortical seizures, and cortical seizures alone. In each case, the cortical seizures were monotonous, and no patient had multiple types of these kinds of seizures.

Gelastic seizures were present in five of six. These seizures were characterized only by desynchronization in the scalp EEG, with no spike activity. In addition, in four patients, other type of seizures suggesting either frontal (three) or temporal (one) origin were recorded. In the cases

TABLE 1. *Clinical data*

	Age (yr)	Sex	Spike activity	Gelastic seizures	Other seizures	Behavioural disturbances	Cognitive development
Patient 1	9	M	Frontal lobe spikes	Yes	Postural seizures	Agression	Learning problems
Patient 2	6	M	Temporal lobe spikes	Yes	Partial complex	Hyperactivity and aggression	Slow language acquisition
Patient 3	9	M	Frontal lobe spikes	Yes	Postural seizures	No	Normal
Patient 4 ^a	25	M	Frontotemporal spikes	No	Partial complex, astatic	Psychotic episodes	Severe mental slowing
Patient 5 ^a	11	M	Frontal lobe spikes	Yes	Astatic, dacrytic	No	Severe learning problems
Patient 6 ^a	5	F	Frontal lobe spikes	No	Partial complex, astatic	No	Normal
Patient 7 ^a	2	F	Temporal lobe spikes	Yes	Partial complex	Hyperactivity	Normal

^aFrom reference 3, with permission.

with frontal involvement, the ictus lasted <30 s, and patients had tonic posture of the four limbs and eyes in two cases and a sudden motor slowing with blank stare and lack of reactivity lasting 5–10 s in another. The ictal recordings showed a lateralized activity to the side of the hamartoma implantation in the hypothalamus in two cases, whereas it was not lateralized in the remaining one. In the patients with temporal lobe seizures, the event lasted ≥ 1 min, and the main features were motor automatisms with lack of reactivity. The ictal EEG showed lateralized temporal lobe spike activity in one patient, and lateralization could not be determined in the other two because these types of seizures did not happen during monitoring.

With respect to the anatomic configuration of the hamartoma, three categories of cases were established: (a) in the four cases in which the structure of the mamillary bodies was preserved (Fig. 1), the predominant interictal spike activity was limited to the frontal lobes, and ictal events were compatible with frontal lobe seizures (Table 1); (b) in the two cases with only connection to the posterior area (Fig. 2), including the mamillary bodies, the interictal spike activity was temporal, and the ictal events suggested temporal lobe involvement; and (c) in the case with apparent simultaneous connection to the posterior and middle areas, no ictal events could be recorded, but the interictal EEG showed frontal and temporal spike activity.

DISCUSSION

This study shows that there is a strong relation between the anatomic characteristics of the hamartoma connection

to the hypothalamus, the spike activity on the EEG, and the cortical epileptic manifestations present in these patients.

The three cases with neurophysiologic and clinical features of temporal lobe epileptic activity had connection of the hamartoma to the mamillary body, suggesting that in these patients, the projection of the paroxysmal activity to the cortex is made through a specific pathway connecting the hypothalamus with the temporal lobe. An antidromic propagation of spike activity through the fornix to the origin of commissural fibers in the subiculum, associated with spread throughout the various projections of the commissural fibers to other mesial temporal lobe areas such as the entorhinal cortex (8), provides such a direct and selective pathway and could be the explanation of the restricted cortical involvement in such patients.

In the four cases with only frontal lobe epileptic activity, the hamartomas were attached to the middle area of the hypothalamus in its more medial subdivision, sparing the mamillary bodies. The existence of direct projections of several neuronal groups in the middle and posterior supramamillary hypothalamus to the frontal lobes (bilaterally) have been described (10,11), which could provide such a selective propagation of spike activity. The connection of the hamartomas to the medial hypothalamus would explain the preferential involvement of topographically organized projection pathways over the more diffusely projecting ones that are more laterally placed (11).

A good correlation was found between the clinical manifestations, suggesting either frontal or temporal lobe involvement and the interictal spike distribution on the scalp. The ictal information is generally compatible but not so

TABLE 2. *Anatomic and neurophysiologic data*

	Lateralization	Volume (cc)	Middle hypothalamus	Posterior hypothalamus	Neocortical seizures	Interictal EEG	Ictal EEG
Patient 1	Right	0.4	Yes	No	Frontal	Frontal (right)	Frontal (right)
Patient 2	Left	0.8	No	Yes	Temporal	Temporal (left)	Not recorded
Patient 3	Left	2.6	Yes	No	Frontal	Frontal (bilateral)	Frontal (left)
Patient 4	Right	2.5	Yes	Yes	—	Frontal/temporal	Not recorded
Patient 5	Right	0.8	Yes	No	Frontal	Frontal (bilateral)	Not recorded
Patient 6	Bilateral	1.3	Yes	No	Frontal	Frontal (bilateral)	Frontal (bilateral)
Patient 7	Right	2.5	No	Yes	Temporal	Temporal (right)	Temporal (right)

complete, as we were not able to record cortical seizures in all patients (Table 2).

Overall the hamartomas in our patients were all sessile and ranged in size from 0.4 to 2.6 cc, which are general characteristics found in series of epilepsy associated with HHs (2,5–8,12,13). No correlation could be drawn between the size of the lesion, the clinical manifestations (Table 1), and the frequency of seizures, which suggests that this is not a good predictor of disease activity.

No detailed analysis of the connection of the hamartoma to the mamillary bodies was reported in the literature, largely because of the lack of spatial resolution of the imaging methods available. Nevertheless, incidental reports of patients with hamartomas connected to the mamillary bodies showed clinical and EEG manifestations of temporal lobe epileptic activity: Patient 1 of List et al. (14) showed clinical and EEG features of left temporal lobe seizures and had a large HH connecting to the left mamillary body demonstrated at autopsy. Patients 1, 4, and 5 of Valdueza et al. (7) showed such a connection and also clinical and EEG features suggesting temporal lobe epilepsy. Patients 3 and 4 in the series of Berkovic et al. (4) also expressed temporal lobe epilepsy in association with mamillary body involvement. Patient 2 of Striano et al. (6) showed both partial complex seizures, temporal lobe spike activity, and a sessile hamartoma extending to the mamillary bodies. In addition, no clear cases of hamartomas with connection to the mamillary bodies were reported without evidence of temporal lobe epileptic activity.

When the hamartoma connects to the hypothalamus, sparing the mamillary bodies, the spike activity appears to be predominant in frontal areas, and the clinical manifestations also are suggestive of frontal lobe epilepsy. A similar trend is apparent in the cases from the literature: The patient of Nishio et al. (15) had such a lesion and frontal spike activity that resolved after surgical removal of the hamartoma; patient 2 of Tasch et al. (16) showed left frontotemporal and generalized spike activity with a hamartoma connecting to the left middle hypothalamus. Patient 1 of Striano et al. (6) had right frontal spike activity and a right side hamartoma with connection to the middle hypothalamus.

The interictal spikes in the scalp EEG are good predictors of the cortical lobe involvement in seizure activity (Table 1), and their disappearance after successful removal of the hamartoma (15) suggests that they are causally related.

Overall the present data suggest that the details of the anatomic connection of the hamartoma to the hypothala-

mus play a significant role in the neocortical spread of spike activity. This spread probably takes place through specific hypothalamic–neocortical pathways, and the neocortical areas affected can be outlined by the scalp distribution of interictal spikes. Confirmation of this model would open surgical alternatives targeting these propagation pathways instead of the removal of the hamartoma in high-risk patients.

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