Electro-clinical manifestations of the epilepsy associated to the different anatomical variants of hypothalamic hamartomas

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***Abstract* – Objective :** The epilepsy associated with hypothalamic hamartomas (HH) presents tipical clinical, electrophysiologic and behavioural manifestations making a caracteristic syndrome, refractory to drug therapy and with unfavourable 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. The authors try to correlate anatomical details of the hamartoma and the clinical/neurophysiological manifestations of the epilepsy in HH.

Methods : The hamartomas of 7 patients with HH and epilepsy (ages 2-25) were classified as to lateralization and connection to the antero-posterior axis of the hypothalamus in high resolution brain magnetic ressonances. We correlated the anatomic classification with the clinical and neurophysiological manifestations of the epilepsy as evaluated in long-term (1-3 days) video-EEG recordings, including ictal documentation.

Results : The hamartomas ranged in size from 0.4 to 2.8 cubic centimeters, with complete lateralization of the connection to hypothalamus in 6/7 of patients. Ictal clinical manifestations showed good correlation with the lobar involvement suggested by the ictal/interictal EEG. These manifestations suggest the existence of two types of neocortical involvement, one associated with temporal lobe, associated with hamartomas connected to the posterior hypothalamus, and another associated with the frontal lobe, seen in lesions connecting to the middle portions of the hypothalamus. Consideration of the known anatomy of the hypothalamic-neocortical projection pathways leads us to suggest propagation of the epileptic activity to the temporal lobes through the Fornix and to the frontal lobes through the Medial Longitudinal Fasciculus.

Conclusions : The unilateral connection to the hypothalamus in most hamartomas along with the propagation of paroxysmal activity to the neocortex through specific anatomic pathways suggests the possibility of performing distal disconnection procedures as a palliative surgical procedure in high risc patients for removal of the hamartoma.

I. INTRODUCTION

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. While the latter is associated with epilepsy, the former is only associated 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.

Several series of patients with this type of epilepsy [3,4,5] displayed diverse clinical and neurophysiological manifestations, along with a large variability in the macroscopic characteristics of the lesion [6]. No study however has established a clear correlation between the detailed anatomical characteristics of the hamartomas and the clinical manifestations in a series of patients.

In this we characterize a series of patients with epilepsy and HH, from a clinical, neurophysiological and anatomical point of view and try to correlate the results with the present knowledge of the organization of the hypothalamic-neocortical pathways.

II. SUBJECTS AND METHODS

The patient population consisted of 7 cases with epilepsy and hypothalamic hamartoma that were evaluated at the clinical neurophysiology laboratory of the Hospital Fernando Fonseca. All had refractory focal epilepsy and were being considered for epilepsy surgery.

The diagnosis of the hamartoma was based on Magnetic Ressonance 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.

In order to improve the anatomical characterization of the lesion, high resolution 3D T1 images were obtained of the whole brain, allowing visualization in perpendicular planes to better understand the connection of the hamartoma to the hypothalamus, as well as inspection of the cortex for associated lesions.

All patients were submitted to long-term (24 to 48 hours) continuous video-EEG, using 27-32 electrodes, and in 6 out of 7, multiple seizures were recorded. At the end of the studies the 3D position of the scalp electrodes was determined in relation to the fiducial points (nasion and pre-auricular points).

The hamartoma connection to the middle and posterior segments of the hypothalamus (Fig.1 and 2) was determined (Table I). The involvement of the mammillay bodies was accepted when there was an interruption on the halo of hypersignal 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 mammillary bodies did not change.

The ictal clinical and neurophysiological data was also determined and tabulated along with the interictal EEG features (Table I).

The correlation between the ictal-interictal EEG features, the seizure characteristics and the anatomical details of the connection to the hypothalamus was investigated.

III. RESULTS

In 6 out of 7 patients the hamartoma connected either to the left or right hypothalamus (Table I). The volume of the lesion ranged from 0.4 to 2.6 cubic centimeters, but all lesions had a sessile attachment to the middle or posterior hypothalamus. In 3 patients the hypothalamic connection was established only in the middle area, while in 2 there was only a connection to the posterior areas (mammillary bodies) (Table I).

The interictal EEG revealed a consistent lobar involvement in each patient, that could be either temporal (3/7) or frontal (5/7). 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 (3/3).

Several ictal events were recorded in 6/7 of the patients. Gelastic seizures were present in 5 out of 6. These seizures were characterized only by desynchronization in the scalp EEG, with no spike activity. In addition in 5 patients other type of seizures suggesting either frontal (3) or temporal (2) origin were recorded, with rhythmical spike activity in the scalp EEG that was concordant with the lobar involvement of the interictal paroxysms (Table I). In the cases with frontal involvement the ictal recordings showed a lateralized activity to the side of the hamartoma implantation in the hypothalamus in 50% of the cases while it was not lateralized in the remaining ones.

With respect to the anatomical configuration of th hamartoma 3 cattegories of cases were established. (a) in 5/6 of the cases where the hamartoma connected to the medium hypothalamus the predominant interictal spike activity was limited to the frontal lobes (Table I); (b) In 3/3 cases with connection to the posterior area (mammillary bodies) the interictal spike activity was temporal and the ictal events suggested temporal lobe involvement; (c) In two cases with simultaneous connection to the posterior and medium areas, one had temporal lobe interictal and ictal events only and in the other no ictal events could be recorded, but the interictal EEG showed frontal and temporal spike activity (Fig.1).

IV. DISCUSSION

This study shows that there is that there is a strong relationship between the anatomical characteristics of the hamartoma connection to the hypothalamus, the scalp paroxysmal EEG and the neocortical epileptic manifestations present in these patients. The 2 cases with

neurophysiological and clinical features of temporal lobe epileptic activity had connection of the hamartoma to the mamillary bodies (posterior hypothalamus), suggesting that in these patients the projection of the paroxysmal activity to the neocortex could be made through the Fornix, that connects the hippocampus to the hypothalamus. All 5 cases with frontal lobe epileptic activity the attachment involved the medial area of the hypothalamus, suggesting as a possible route for the propagation of epileptic discharges the Medial Longitudinal Fasciculus.

Overall the hamartomas in our patients were all sessile and ranged in size from 0.4 to 2.6 cubic centimeters, which are general characteristics found in series of epilepsy associated to HH [2,4,5,6,7,8]. No detailed analysis of the connection of the hamartoma to the mammillary bodies was reported in the literature, largely due to the lack of spatial resolution of the imaging methods available. Nevertheless there have appeared incidental reports of patients with hamartomas connected to the mammillary bodies showing clinical and EEG manifestations of temporal lobe epileptic activity : Patient 1 of List et al (1958) [9] showed clinical and EEG features of left temporal lobe seizures and had a HH connecting to the left mammillary body demonstrated at autopsy; Patient 1, 4 and 5 of Valdueza et al. (1994) [6] 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. (1988) [3] also expressed temporal lobe epilepsy in association with mamillary body involvement; Patient 2 in Striano et al. (1999) [5] 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 mamilary bodies were reported without evidence of temporal lobe epileptic activity.

When the hamartoma connects to the hypothalamus in its middle portion however, the spike activity appeared to be predominant in frontal areas and the clinical manifestations were also suggestive of frontal lobe epilepsy. A similar trend is apparent in the cases from the litterature : The patient of Nishio et al (1994) [10] had such a lesion, and frontal spike activity that resolved after surgical removal of the hamartoma; Patient 2 of Tasch et al (1998) [11] showed left fronto-temporal and generalized spike activity with a hamartoma connecting to the left medial hypothalamus; Patient 1 of Striano et al (1999) [5] 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 neocortical lobe involvement in seizure activity (table I) and their disapearance after successful removal of the hamartoma [10] suggests that they are causally related.

Overall the present data suggests that the details of the anatomical connection of the hamartoma to the hypothalamus plays 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 risky removal of the hamartoma.

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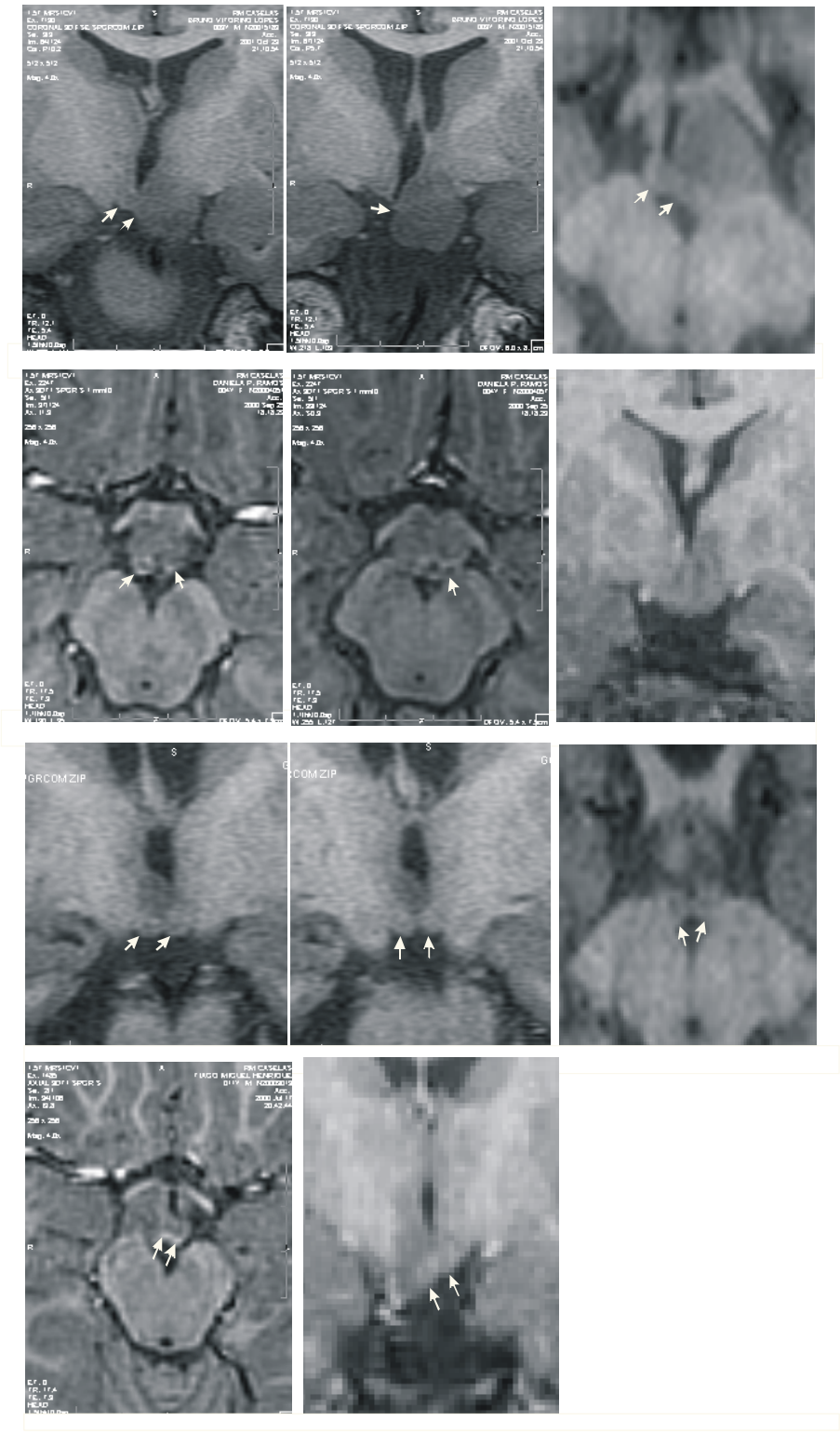

Fig. 1 - MRI details of the relation between the hamartoma and the hypothalamus in the cases where the lesion does not change the structure of the mamillary bodies (white arrows). Each row represents a patient (from above, patients 2, 6, 3 and 5). Patient 2 shows a large left side hamartoma that shifts the position of the mamillary bodies in the two coronal and one axial view. Patient 6 has a bilateral implantation in the middle hypothalamus, while sparing the mamillary bodies in the two axial and one coronal slices shown. Patient 3 has a small right side hamartoma also sparing the mamillary bodies in the two coronal and one axial views shown. For patient 5 the axial and coronal views show a right side hamartoma shifting but not connecting to the mamillary bodies.

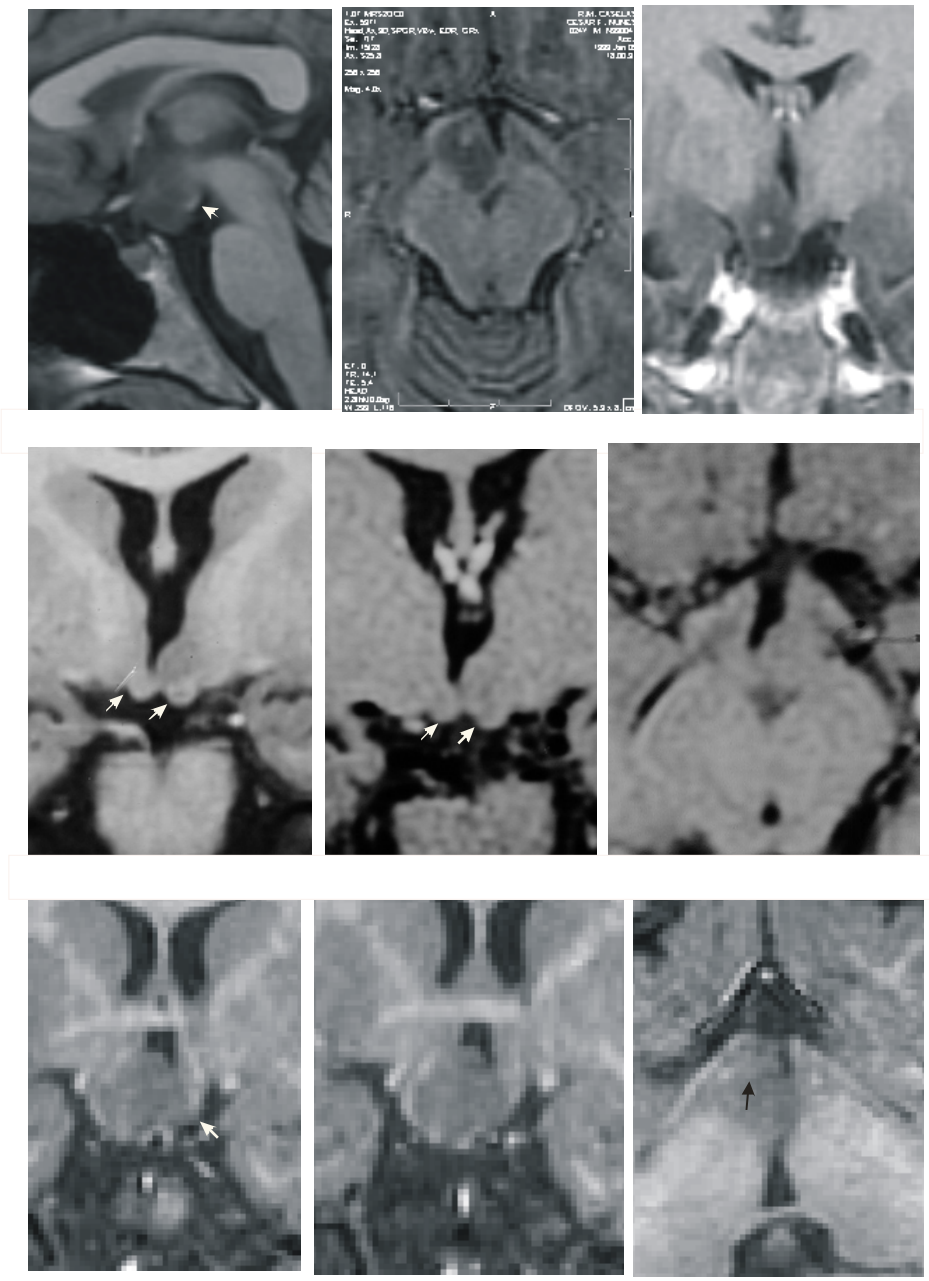

Fig. 2 - MRIs of the patients with hamartoma connecting to the mamilary bodies (white arrows). Each patient is represented in a row, from above : patient 1, patient 7 and patient 4. For patient 1 a large, right side, lesion connects both to the middle hypothalamus and to the mamillary body in the sagital, axial and coronal planes shown. For patient 7 the hamartoma shows connection to the left mamillary body in the two coronal and one axial views. A large right side hamartoma connecting to the homolateral mamillary body and sifting the middle hypothalamus in the anterior direction (black arrow on the right side axial view).

Table I

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age	25	9	8	2	11	5	6
Sex	male	male	male	female	male	female	male
Lateralization	Right	Left	Right	Right	Right	Bilateral	Left
Volume*	2.5	2.6	0.4	2.5	0.8	1.3	0.8
Middle hypoth.	Yes	Yes	Yes	No	Yes	Yes	No
Posterior hypoth.	Yes	No	Yes	Yes	No	No	Yes
Gelastic seizures	No	Yes	Yes	Yes	Yes	No	Yes
Neocortical seizures		Frontal	Frontal	Temporal	No	Frontal	Temporal
Interictal EEG	Frontal/temporal	Frontal	Frontal	Temporal	Frontal	Frontal	Temporal
Ictal EEG	-	Frontal	Not focal	Temporal	Not focal	Frontal	Not focal

* cubic centimeters