



Hypothalamic Hamartomas—What Determines Seizure Types and Other Clinical Manifestations?

Gelastic Epilepsy and Hypothalamic Hamartomas: Neuroanatomical Analysis of Brain Lesions in 100 Patients.

Parvizi J, Le S, Foster BL, Bourgeois B, Riviello JJ, Prenger E, Saper C, Kerrigan JF. *Brain* 2011;134:2960–2968.

Hypothalamic hamartomas present with isolated fits of ictal laughter (gelastic epilepsy) or a combination of gelastic and other types of seizures. Many of these patients also suffer from cognitive decline, neuropsychiatric comorbidities and precocious puberty. Although there is a large body of anecdotal evidence about hypothalamic hamartomas and gelastic seizures, many questions still remain to be answered. For instance, which specific hypothalamic regions are most affected by the location of hamartomas causing laughing versus other types of seizures? Does the neuroanatomical localization of the lesions differ in cases with only gelastic seizures or a combination of gelastic and other types of seizures? Does the location of the lesions correlate with the presence of precocious puberty, and does the type of lesion influence the severity or the type of seizures? In a retrospective review of clinical and structural neuroimaging data from 100 cases of gelastic epilepsy and hypothalamic hamartoma, we aimed to address these questions by analysing the clinical presentation and the neuroanatomical features of the hypothalamic lesions in these patients. Our findings suggest that in all 100 cases, lesions were centred at the level of the mammillary bodies in the posterior hypothalamus. Compared with the patients with pure gelastic seizures ($n = 32$), those with gelastic and other types of seizures ($n = 68$) had significantly longer duration of epilepsy ($P < 0.001$), whereas age of seizure onset, the volume of lesions and the proximity to the mammillary bodies were not different between the two groups. In contrast, patients with cognitive or developmental impairment and those with precocious puberty had significantly larger lesions involving the anterior and posterior hypothalamus.

Commentary

The association of gelastic seizures and hypothalamic hamartoma is a striking example of intrinsic epileptogenicity in a subcortical lesion. Gelastic and other seizures are often frequent and drug-resistant, prompting evaluation for epilepsy surgery. Seizure origin was erroneously attributed to temporal or frontal cortex, and outcome of surgical resections in these areas was uniformly unfavorable (1). Several lines of evidence made it clear that gelastic seizures are generated from the hypothalamic hamartoma itself. Ictal onset was recorded in the hypothalamic hamartoma by depth electrode recordings, and gelastic seizures were reproduced by electrical stimulation of the hamartoma (2, 3). In addition, ictal SPECT showed hypothalamic hyperperfusion (2). The intrinsic epileptogenicity of the hamartoma was further proven by the favorable outcome of therapeutic intervention directed at the hamartoma itself (4).

The clinical manifestations of hypothalamic hamartomas are not uniform. Not all patients have seizures; some present to medical attention because of precocious puberty. Among those who do have seizures, fewer than half have precocious

puberty. Cognitive impairment is another variable; it may also change over time or develop over the course of the associated epilepsy. Although almost all patients with epilepsy have gelastic seizures, at least at onset, other seizure types may coexist, including complex partial and generalized tonic-clonic seizures. Some patients even develop epileptic encephalopathy such as Lennox-Gastaut syndrome with generalized tonic and atonic seizures. Parvizi and colleagues evaluated the anatomical correlates of clinical manifestations of hypothalamic hamartomas in patients referred to the Barrow Neurological Institute Hypothalamic Hamartoma Center for surgical management of epilepsy. They found that the hamartomas were consistently close to the mammillary bodies and extended posteriorly to the mammillary body coronal plane, suggesting that involvement of the posterior hypothalamus was necessary for development of gelastic seizures. Other studies suggested that epilepsy was associated with “intra-hypothalamic” localization of the hamartoma with a vertical plane of attachment to the hypothalamus within the third ventricle, with distortion of the ventricle (5). Seizures were absent when the hamartoma was “parahypothalamic,” only attached to, or suspended from, the floor of the third ventricle (5). The study of Parvizi and colleagues seemed to support this finding. Using the Delalande classification of hamartomas, they found that 86 percent of hamartomas were of type II or III, which include a vertical



plane of attachment within the third ventricle. The authors did not indicate how many of the remaining 14 percent had type IV (giant hamartoma) or type I (hamartoma with only horizontal attachment to the floor of the third ventricle).

Parvizi and colleagues also found that a large hamartoma size predicted precocious puberty. However, their study only included patients with epilepsy and cannot be extrapolated to the general population of patients with hypothalamic hamartomas. In fact, hamartomas associated with isolated precocious puberty tend to be smaller than ones associated with epilepsy. One study found that none of 18 patients with a hamartoma diameter less than 10 mm had seizures (6). Another study that compared nine patients with isolated precocious puberty and four patients with isolated seizures found that the former had small hamartomas suspended from the floor of the third ventricle, while the latter had larger hamartomas in the interpeduncular cistern (7). Hamartomas associated with pure precocious puberty also tend to be anterior hypothalamic. Because posterior involvement at the level of the mammillary bodies was needed for seizures, this explains why patients with both seizures and precocious puberty had larger hamartomas with larger anterior-posterior dimension than did patients with seizures and no precocious puberty.

In the study of Parvisi and colleagues, there was no relation between seizure type or seizure severity and hamartoma size, location, orientation, or surface area attachment. Only longer duration of epilepsy predicted presence of seizure types other than gelastic seizures. Hypothalamic hamartomas do not grow significantly, and size of the hamartoma had no relationship to the duration of epilepsy. The appearance of other seizure types over time suggests a process of secondary epileptogenesis. This process may involve development of new or altered seizure networks, facilitating seizure spread beyond the hypothalamus. The notion of evolution of the epilepsy is supported by video-EEG analysis of seizure semiology in patients with hypothalamic hamartomas (8). In a study of 31 patients with hypothalamic hamartoma and epilepsy, secondarily generalized seizures occurred in adolescents and adults but did not occur in children. In addition, the gelastic component was longer and overall seizure duration shorter in children than in adults and adolescents (8).

The evidence of progression of epilepsy highlights the need for early effective treatment of hypothalamic hamartomas associated with seizures. The most definitive treatment modalities are surgical removal through a transcallosal interforaminal approach (9) or with endoscopic surgery (10) or surgical disconnection (11). The expected seizure-free rate is 47 to 58 percent (4). Stereotactic radiofrequency thermocoagulation and radiosurgery are associated with lesser seizure-free rates and are less successful with larger lesions, but being less invasive, can be considered for management of residual hamartomas in patients who failed earlier resection (12, 13). Radiosurgery is less invasive than other approaches but has the disadvantage of delayed efficacy (12). With improved

surgical techniques, earlier resective surgery is recommended to avoid worsening epilepsy and associated cognitive and psychiatric deterioration.

by *Bassel W. Abou-Khalil, MD*

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