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Status Gelasticus after Temporal Lobectomy: Ictal FDG-PET Findings and the Question of Dual Pathology Involving Hypothalamic Hamartomas

*†Andre Palmini, †Wim Van Paesschen, †Patrick Dupont, †Koen Van Laere, and †Guido Van Driel

**Neurology Service & Epilepsy Surgery Program, Hospital São Lucas da PUCRS, Porto Alegre, Brazil; and †Departments of Neurology and Nuclear Medicine, University Hospital Gasthuisberg, Katholiek Universiteit Leuven, Leuven, Belgium*

Summary: *Purpose:* To present the first ictal fluorodeoxyglucose–positron emission tomography (FDG-PET) evidence of the hypothalamic origin of gelastic seizures in a patient with a hypothalamic hamartoma (HH) and to raise the issue of *true* dual pathology related to this entity.

Methods: Ictal FDG-PET was acquired during an episode of status gelasticus with preserved consciousness, in a patient previously operated on for complex partial seizures (CPSs) due to a temporal lobe epileptogenic cyst.

Results: Ictal hypermetabolism was localized to the region of the HH during the status gelasticus. CPSs had been completely eliminated after temporal lobe surgery.

Conclusions: Ictal FDG-PET independently confirmed that gelastic seizures in patients with HH do originate in the diencephalic lesion. An HH may coexist with another epileptogenic lesion, in a context of dual pathology. **Key Words:** Status gelasticus—Hypothalamic hamartoma—Ictal FDG-PET—Temporal lobe epilepsy—Dual pathology.

Interest in the relation between hypothalamic hamartomas (HHs) and epilepsy has been increasing in the last few years, driven by a better delineation of the different syndromes involved and their surgical remediation (1–5). Moreover, clinical evidence suggests that these diencephalic lesions lead to localized or diffuse secondary epileptogenesis, thus opening a window of research on the neurophysiologic mechanisms underlying partial and generalized epilepsies (6–8). A key to this understanding is the fact that these deep-seated lesions have been shown to be themselves the generator of gelastic (laughing) seizures (4,9,10) and also that their resection is crucial for the control of complex partial, generalized, and other seizures (1,4,5,7) that are often part of the epileptic disorder.

Previous to the current understanding of the direct and indirect epileptogenic roles of HH, several groups have made attempts to control the medically refractory complex partial and secondarily generalized seizures through resection of cortical regions identified during preoperative evaluation. Ictal and interictal EEGs obtained with both scalp/sphenoidal and depth electrodes often showed irritative and ictal-onset zones in temporal and frontal lobe structures (11,12). These findings were even confirmed by interictal fluorodeoxyglucose (FDG) positron emission tomography (PET) studies, and thus cortical resections "ignoring" the role of the deep-seated hamartoma seemed a sound strategy. However, such resections have consistently failed, and histopathologic examination of resected tissue has not identified independent cortical pathology (11,12).

The gears are now shifted in the opposite direction: whenever medically refractory seizures are present in patients with HH, the best strategy is to resect the diencephalic lesion, in the expectation that all seizure types will be controlled. This is now an established surgical strategy (4,5,7,13,14), although many questions remain about the exact nature of the relations between the HH and interconnected cortical regions.

We herein report a unique patient whose neuroimaging findings and clinical evolution both confirm and challenge some of the concepts mentioned. On the one hand, we provide for the first time ictal FDG-PET confirmation that gelastic seizures indeed originate in the HH. On the other hand, we show that cortical resections have a place in selected patients with HH and complex partial seizures when another unrelated pathology is present.

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Address correspondence and reprint requests to Dr. A. Palmini at Serviço de Neurologia, Hospital São Lucas da PUCRS, Avenida Ipiranga 6690, CEP 90610-000, Porto Alegre, RS, Brazil. E-mail: apalmini@uol.com.br

CASE REPORT

In this 35-year-old man, epilepsy developed at the age of 10 years. His gestation and birth were uneventful, and his early development was normal. No history was noted of cerebral trauma, febrile convulsions, or meningoencephalitis. He initially had a few secondarily generalized tonic–clonic seizures, which remained well controlled with antiepileptic drugs (AEDs). Simple partial seizures were characterized by a rising epigastric sensation and nausea, lasted around a minute, and occurred daily. At age 32 years, his seizures became more severe, and although he remained conscious during the attacks, he felt disoriented for a few minutes afterward. Because the seizures remained refractory to different AEDs in maximally tolerated doses, he underwent presurgical evaluation.

Physical and neurologic examinations were normal. A high-resolution magnetic resonance imaging (MRI) scan of the brain showed a large subarachnoid cyst in the left medial fossa. During video-EEG registration, four of the habitual temporal lobe seizures were recorded. These were characterized by staring and manual automatisms in an otherwise responsive patient, who was able to talk during the seizures. Interictal EEGs showed epileptic activity over the left anterior and midtemporal regions, and ictal scalp EEGs displayed a recruiting theta rhythm over the left mid- and posterior temporal lobe. Two ictal single-photon emission computed tomography (SPECT) studies showed hyperperfusion in the left temporal lobe, posterior to the subarachnoidal cyst. A Wada test indicated that language centers were shifted to the right hemisphere. He underwent a resection of left temporal neocortex and marsupialization of the arachnoid cyst. Pathological examination of the resection specimen revealed arachnoid membranes and mild gliotic changes in the temporal neocortex. The temporal lobe seizures have not recurred for 3 years since the operation.

The immediate postoperative period was complicated by a status gelasticus, in which gelastic seizures lasting $\leq$20 s recurred every 1–5 min. The seizures were characterized by uncontrollable laughter, which the patient experienced as pleasant and genuine. The longest episode of laughter lasted 1 h. According to the patient, he had experienced short-lasting episodes of sudden and uncontrollable laughter for as long as he could remember, but had not considered these abnormal. A postoperative MRI revealed a small HH of $\sim$8 mm in diameter, which had been overlooked on the preoperative scans (Fig. 1). An FDG-PET was performed during the status gelasticus, with gelastic seizures lasting $\sim$20 s and recurring every 2 min. The patient remained fully conscious during these episodes and was able to keep his head motionless on the PET table. The FDG-PET showed an intense hypermetabolism in the

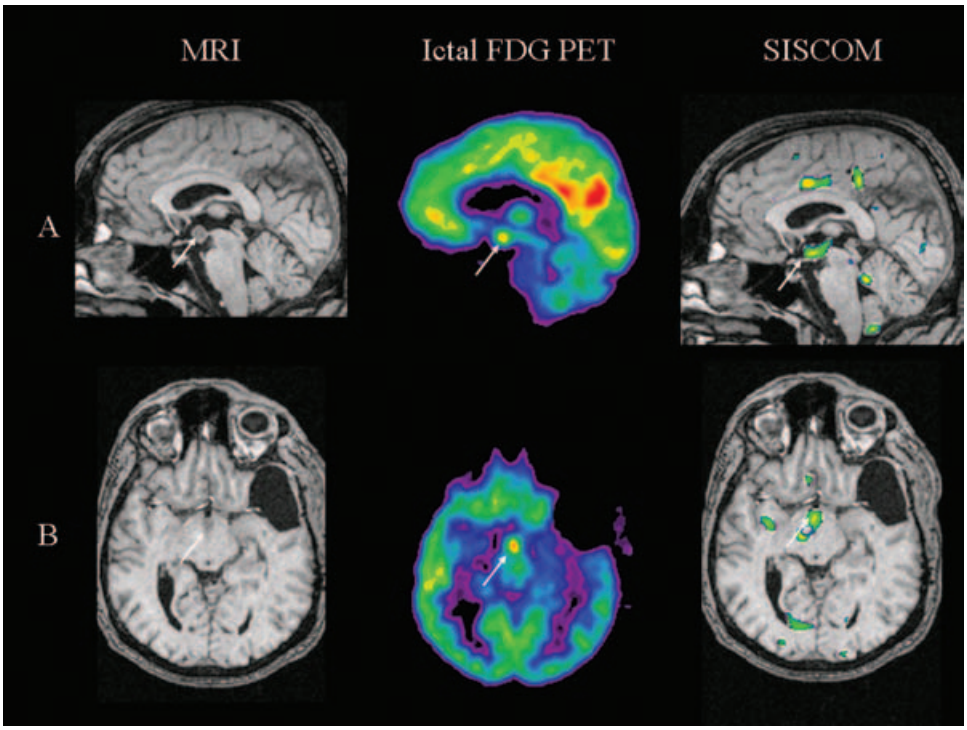

FIG. 1. Magnetic resonance images (MRI), ictal fluorodeoxyglucose-positron emission tomography (ictal FDG PET) and ictal subtraction single-photon emission computed tomography co-registered with MRI (SISCOM) in the midline sagittal (A) and axial (B) planes showed ictal hypermetabolism and hyperperfusion in the region of the hypothalamic hamartoma (white arrows). Note also previous resection of the left anterior temporal lobe.

HH (Fig. 1). An ictal SPECT, with injection initiated 2 s after onset of a simple partial gelastic seizure that lasted 21 s, showed mild hyperperfusion in the HH (Fig. 1). Interictal and ictal EEGs did not show epileptic changes. He was treated with carbamazepine (CBZ), 400 mg b.i.d. A spontaneous running-down phenomenon occurred, and 4 months after the operation, he experienced one gelastic seizure per day that lasted ~5 s. Three years after the operation, he experienced only an urge to laugh once every week. He was able to resume his work as a process operator and is driving a car.

DISCUSSION

The patient we report is cured of his complex partial seizures after temporal lobectomy and marsupialization of an arachnoid cyst in the left temporal lobe, despite the presence of an HH that was not identified preoperatively. The presence of a dysfunctional and truly epileptogenic left temporal lobe could be inferred before surgery by the shift in language dominance, the temporal lobe–type semiology of the complex partial seizures, the ictal SPECT findings, and the consistent ictal and interictal epileptiform abnormalities present in that temporal lobe. It was confirmed by the achievement of seizure control after temporal lobe surgery. Admittedly, arachnoid cysts, such as the one associated with the left temporal lobe epilepsy in our patient, are often incidental findings (15), although a rare association with HH has been reported (16). They could be simply a marker of some other developmental or posttraumatic abnormality in the adjacent cortical regions displaying epileptogenic abnormalities. However, irrespective of the later evolution of this patient, the present observation suggests that when convergent clinical, interictal, and ictal neurophysiological abnormalities colocalize with cortical regions adjacent to arachnoid cysts, the latter may be potentially regarded as epileptogenic lesions.

To our knowledge, this is the first case in which complex partial seizures were controlled by cortical resection in patients with an HH. Similar patients may exist, in whom an HH passed unnoticed, and postoperative imaging was never performed. However, because either gelastic attacks or so-called episodes of "pressure to laugh" are present in the vast majority of patients reported to date with HH and epilepsy (1,2), the postoperative persistence of these seizures must have been overlooked. Otherwise, imaging would have been repeated and the lesion found, as was the case with our patient.

The evolution of this patient indicates that cortical resections should not be a priori excluded as a surgical strategy when another potentially epileptogenic cortical lesion is found, simply because an HH is present. Although the latter is rare, a high index of suspicion must be present when evaluating patients with both gelastic and complex partial seizures. As has been shown in patients with dual pathology, particularly those with hippocampal sclerosis associated with other neocortical lesions (17), complete seizure control is much more likely when the two epileptogenic lesions are resected. Thus the persistence of the previously unidentified gelastic seizures after resection of the cyst and adjacent temporal lobe structures in our patient should indeed be expected.

Another interesting point is whether we would have proceeded with the same preoperative investigative procedures and the same surgical strategy should the HH have been identified beforehand. The presence of the cyst and the shift in language dominance would probably suggest that temporal resection was warranted. However, the neurophysiological findings of temporal lobe seizure onset, per se, in a patient with an associated HH, would not be indicative that a temporal resection would bring complex partial seizures under control (11,12). Although it is difficult to discuss retrospectively the "gestalt" underlying the decision-making process in epilepsy surgery, should the presence of the HH be known beforehand, the decision to move forward with a temporal resection would be going against the consensual view that only resecting the HH would count. One of the puzzles of the epilepsies related to HH is that, even though only the gelastic seizures truly originate in the diencephalon, resection of the lesion seems pivotal also for seizure alleviation of those seizures that originate in the cortex (4,5,7). The fact that this patient was successfully managed in a different fashion is the whole point of this report and highlights the need to tailor carefully the presurgical evaluation and the surgical approaches when another cortical lesion is present in a patient with epilepsy and HH. In theory, intracerebral depth electrodes probing from both lesions should be able to detect independent seizure onsets in the HH and in the left temporal lobe. In that sense, it could be expected that the presence of dual pathology in the patient reported here would demand resection of both lesions for control of the two different types of seizures. Thus the management of epilepsy associated with two different lesions, one of which is an HH, may not differ from the management of the more classic dual pathology in which a cortical lesion is associated with unilateral hippocampal sclerosis (17). The favorable evolution of this patient in terms of control of the temporal lobe–type complex partial seizures, coupled with the persistence of the gelastic seizures, strongly suggests that this patient had not only two different lesions but also two different epilepsies. The possibility that this may occur in patients harboring an HH should be considered.

The frequent epileptiform discharges recorded in the temporal lobes of patients with HH can be attributed to the dense connectivity between these two structures, and the sudden occurrence of status gelasticus after temporal lobe resection in our patient, without any change in AEDs, suggests an acute disinhibitory phenomenon, further supporting the relevance of temporohypothalamic

connections. It is likely that hypothalamic reorganization from the acute disinhibition led to a running down of the gelastic seizures, to a point at which these hardly interfered with the patient's life.

That the remaining gelastic seizures originate from the HH itself was shown both by ictal FDG-PET and SISCOM (Fig. 1). An ictal PET was possible because the patient was able to cooperate fully during a gelastic status. This finding is unlikely to be easily reproduced; a PET scanning is not indicated in most patients with HH. Nevertheless, PET data may prove useful for the understanding of the relations between the HH and the overlying cortex. It has been recently shown that interictal PET consistently displays areas of cortical hypometabolism in patients with HH, which may be related to a dysfunctional epileptic and nonepileptic network responsible for the nongelastic seizures and the behavioral abnormalities in this disorder (18). In contrast, SISCOM is a simpler method that has been useful for the understanding of the HH/epilepsy syndrome. It is a highly desirable investigation in potential surgical candidates, when resection of the HH is anticipated (5,6,10). In our patient, SISCOM showed a core of hyperperfusion in the region of the hypothalamus, with an extension of the hyperperfusion to other limbic regions, which likely reflects ictal propagation. Other functional imaging methods, such as proton magnetic spectroscopy, also have shown intrinsic abnormalities in the HH that concur with its role in the generation of gelastic seizures (19).

This man belongs to a specific class of patients with HH who are diagnosed only during adulthood, usually because their epilepsy is not severe, cognition is reasonably normal, and the hamartoma is small (1,2,12,20). A continuum of severity of epileptic syndromes seems to be associated with HH, and patients with small lesions may have a more benign course, although lesion size is not the only factor involved in the severity of the condition (1). The recognition of these milder cases is important to explain apparently bizarre symptoms such as "pressure to laugh" (2) and also to allow a more detailed understanding of epilepsy syndromes manifested by complex partial and gelastic seizures. Many patients will not have a second extrahypothalamic pathology, and resection of the neocortical abnormalities will likely fail. However, whenever patients with HH are initially seen with gelastic and other seizure types associated with additional extrahypothalamic lesions, the possibility of independent seizure generation should be considered and approached accordingly. The excellent control of the complex partial seizures achieved by our patient should encourage the search of dual pathology in patients with HH and intractable epilepsy.

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