Deep brain stimulation for the treatment of drug-refractory epilepsy in a patient with a hypothalamic hamartoma

Case report

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Hypothalamic hamartomas (HHs) are developmental malformations associated with a range of neurological problems, including intractable seizures. There is increasing evidence of the epileptogenicity of the hamartoma and of the inhomogeneous distribution of the epileptic abnormalities within the malformation. The management strategy for treatment and results differ according to the insertion plane and the extension of the malformation into the hypothalamus. Cases characterized by extensive involvement of the hypothalamus are particularly challenging.

The authors describe the case of a patient with drug-resistant epilepsy and a large hypothalamic hamartoma with an extensive area of attachment. The patient underwent implantation of 2 deep brain electrodes. The intraoperative recording showed a synchronous interictal epileptic discharge in the left temporal lobe and on the left side of the lesion. The patient was treated with chronic high-frequency stimulation. No side effects due to the stimulation were reported. At 18 months’ follow-up, a reduction in complex partial seizure frequency was reported, but no significant reduction in overall seizure frequency was noticed (p = 0.14, t-test).

The authors report on neurophysiological studies of the relationship between HH and epilepsy, and also discuss the literature on chronic high-frequency stimulation, including its rationale and the results of chronic stimulation of various targets for the treatment of drug-resistant epilepsy due to HH. (DOI: 10.3171/2010.11.FOCUS10241)

Key Words • hypothalamic hamartoma • deep brain stimulation • invasive monitoring • gelastic seizure

Hypothalamic hamartomas are rare developmental malformations associated with a range of neurological and endocrine disturbances, including seizures resistant to antiepileptic medications, cognitive and psychiatric disorders, and precocious puberty.

There is strong evidence that patients with HH and drug-resistant epilepsy benefit from resection or disconnection of the HH, but resective surgery can lead to hypothalamic disturbances, visual field deficits, motor deficits, and thalamic infarcts.27,40 Disconnection by transventricular or transcallosal endoscopic approach has a good outcome and fewer complications than resective surgery.1,8,14,24 There is also strong evidence that radiofrequency and Gamma Knife surgery may lead to complete disappearance of interictal spikes recorded from the hamartoma and from scalp EEG, with reappearance when the stimulation was interrupted.

The authors report that seizures arising from the HH spread to the cortex through the mamillothalamic-cingulate tract. Kahane et al.27 also demonstrated that chronic stimulation of the hamartoma induced a complete disappearance of interictal spikes recorded from the hamartoma and from scalp EEG, with reappearance when the stimulation was interrupted.

We report the case of a patient with an HH and drug-resistant epilepsy treated with high-frequency chronic stimulation by implantation of 2 deep brain electrodes within the malformation.

Case Report

History and Presentation. This 31-year-old right-handed woman was admitted to our hospital for presurgical evaluation for drug-refractory epilepsy associated with an HH.

Epilepsy onset was at 13 years of age with a secondary generalized tonic-clonic seizure during sleep. A few weeks later the patient developed gelastic and complex focal sei-
zures characterized by a pleasant thoracic aura followed by loss of contact, with staring, bilateral gestural, oroalimentary, and deambulatory automatisms. In the postictal phase, a language disturbance was reported. Seizure duration ranged between 20 and 60 seconds; the frequency reported was 3–7 episodes per month, often in clusters of 3–4 successive seizures. Phenobarbital, carbamazepine, vigabatrin, and levetiracetam were not effective in controlling the seizures. The patient’s relevant personal and family medical histories were otherwise unremarkable.

Examination Findings. The results of general and neurological examinations at hospital admission were normal. The patient’s body mass index was 25. The results of a routine blood analysis and a complete hormonal assessment were within the normal range.

The EEG was characterized by normal background activity and interictal epileptic abnormalities in both temporal lobes, with prevalence on the left side. The abnormalities were increased by sleep. A complex focal seizure was recorded: the ictal discharge was characterized by theta-delta rhythmic recruiting activity recorded on the left temporal lobe.

Magnetic resonance imaging showed a retrochiasmatic lesion extending to the anteroinferior part of the third ventricle with a wide insertion into the hypothalamus. The 25-mm lesion was hypointense in T1-weighted images and hyperintense without enhancement in T1-weighted images obtained after Gd administration (Fig. 1).

A complete ophthalmological examination and neuropsychological and psychiatric assessments were performed. All results were normal.

After the presurgical evaluation, resective surgery was refused by the patient. At that point, palliative DBS was proposed and accepted. Informed consent was obtained.

Operation and Postoperative Course. Implantation of the DBS electrodes was performed after induction of general anesthesia. Four-lead DBS electrodes (Medtronic DBS lead 3389, 4 contacts 1.27 mm in diameter, 1.5 mm long, spaced by 0.5 mm) were placed bilaterally by stereotactic technique (Leksell G frame) (Fig. 2).

Intraoperative EEG recording was performed using scalp electrodes and within the lesion using the DBS electrodes (Fig. 3). Synchronous interictal epileptic discharges were recorded from the left temporal lobe and the left side of the lesion. The maximum amplitude of the spikes was observed on the distal contacts of the left DBS electrode (contacts 0–1-2) and on the F7 and T3 scalp electrodes. No interictal epileptic abnormalities were recorded from the right side of the hamartoma.

No early or delayed surgical complications were observed. The postoperative CT scan revealed correct placement of both electrodes within the hamartoma (Fig. 2).

Two days after surgery chronic bilateral unipolar stimulation was started with the following parameters: (case positive; 0–1-2 negative) 90 μsec, 130 Hz, 0.3 V.

The patient maintained a seizure diary for accurate pre- and postoperative seizure frequency evaluation.

Follow-up visits, performed every 3 months, included

![Fig. 1. Preoperative axial, coronal, and sagittal MR images showing the hamartoma with an extensive area of attachment to the hypothalamus. The malformation was hyperintense in T2-weighted images (upper) and hypointense without enhancement in T1-weighted images obtained after Gd administration (lower).](image-url)
body mass index assessment, routine blood studies, complete hormonal assessment, neurological and psychiatric examination, and basal EEG. Within the 1st year after surgery, the amplitude of stimulation was increased at each visit. An amplitude of 2 V was reached at the last follow-up visit without any side effects. No behavioral, endocrinological, or neurological abnormality or abnormal increase in weight was observed at any of the follow-up visits.

After a follow-up period of 18 months, the patient and the family reported a reduction in intensity and frequency of the complex partial seizures. Nevertheless, analysis of the patient’s seizure diary did not reveal a significant reduction in overall seizure frequency (complex partial and gelastic seizures; p = 0.14, Student t-test) (Fig. 4). At 10 months after initiation of stimulation, the onset of reappearance of complex partial seizures was noticed, and at 15 months a hardware failure occurred (the pulse generator spontaneously switched off).

Discussion

Recently, an increasing number of papers dealing with epilepsy in children or adults with HH have been published. Our case confirms that the epilepsy syndrome observed in adults with HH is different from the catastrophic epilepsy that develops in childhood. When epilepsy begins later, learning and behavioral problems are fewer, gelastic seizures are less prominent, and the epilepsy syndrome is usually restricted to 1 or 2 partial seizure types.

The majority of the cases of hamartoma reported were drug refractory, and the resection or disconnection allowed good results and a low complication rate, if surgery was tailored to the anatomical characteristics of the individual patient. According to the classification proposed by Delalande and Fohlen, which categorized HHs into 4 types, surgical outcome is good in patients with Types I, II, and III (Type I, horizontal insertion plane, lesion may be unilateral; Type II, vertical insertion plane and intraventricular location; and Type III, combination of Types I and II), but not good (low rate of seizure freedom) in patients with so-called giant hamartomas (Type IV).

The cognitive, behavioral, and hormonal conditions of our patient were normal, and according to the Delalande classification, the hamartoma was classified as Type IV; a less-invasive treatment, different from resective or disconnective surgery, such as DBS, was suggested.

Invasive neurophysiological studies on the relationship between hamartomas and epilepsy are few and inconclusive. Reports of chronic high-frequency stimulation for the treatment of HH are also limited. Deep brain stimulation surgery is a minimally invasive procedure that allows the perioperative recording of epileptoge-
nicity of the hamartoma, and permits the mapping, by stimulation, of the “symptomatogenicity” of the malformation. In the series of 5 patients with HH reported by Kahane et al.,17 the scalp EEGs showed diffuse interictal and ictal abnormalities; in 4 out of 5 cases the predominant side of the EEG abnormalities was ipsilateral to the activity recorded within the hamartoma. One patient in the series underwent chronic high-frequency stimulation with an unclear reduction of seizure frequency as well as weight gain that reduced when the stimulation was stopped (Table 1).17 The neurophysiological data reported by the Grenoble group were confirmed by our case, which showed interictal epileptic abnormalities in both temporal lobes, with prevalence on the left side, and an ictal discharge arising in the left temporal lobe. In addition, our intraoperative study showed abundant epileptic activity within the hamartoma with the maximum amplitude of the spikes on the left DBS electrode, synchronous with the epileptic abnormalities recorded from the left temporal scalp EEG.

In line with the experience of Munari and Kahane, our data confirm the epileptogenicity of the hamartoma and the nonhomogeneous distribution of the epileptic abnormalities within the malformation.17, 23 Moreover, the symptoms elicited by stimulation of the malformation demonstrated a specific distribution of the epileptogenic areas within the epileptic foci.17, 23 In the 2 cases reported by Khan et al.,19 the EEG findings were not reported, and the unilateral stimulation was effective in reducing the seizure frequency in both cases. This study demonstrates indirectly the findings of Munari and Kahane and their colleagues, and confirms the role of the invasive study for the correct mapping of the epileptic network of the hamartoma.

Waldau et al.39 performed a histopathological study of an HH that had been resected from a pediatric patient with gelastic seizures. The lesion showed only rare, randomly distributed neurons, suggesting that a few solitary neurons in an HH can drive epilepsy.

The rationale for DBS is based on an inhibitory effect on the epileptogenic zone achieved by stimulation of deep brain structures connected with the cortex. As a matter of fact, seizure control could be obtained by activation of all the epileptogenic neurons with supramaximal stimulus intensity. The target of stimulation could be a deep brain structure or a fiber tract connected with the majority of the neurons in the epileptogenic zone.21 The corpus callosum and the fornix could be this kind of target. The fornix connects the hippocampus with the hypothalamus and the mammillary tract; moreover, it is strongly connected with the homologous contralateral fornix. Based on this concept, 2 patients with medically intractable epilepsy secondary to HH were successfully treated by means of unilateral DBS of the MTT. In both patients, the electrode was placed ipsilateral to the hamartoma.19 One patient with complex partial seizures remained seizure free 14 months from surgery; the other patient suffering from gelastic and complex partial seizures showed a seizure frequency reduction of greater than 80%. Both patients had an improvement in their quality of life with the ability to attend full-time school activities.

Among the deep brain structures, the ANT, which

<table>
<thead>
<tr>
<th>AUTHORS &amp; YEAR</th>
<th>AGE AT ONSET</th>
<th>SEX</th>
<th>SZ TYPE</th>
<th>SZ FREQ</th>
<th>PREOP COGNITIVE STATE</th>
<th>DELANDER CLASS</th>
<th>ELECTRODE PLACEMENT</th>
<th>TARGET</th>
<th>ELECTRODE POSITION</th>
<th>ELECTRODE PARAMETERS</th>
<th>RESULTS</th>
<th>SIDE EFFECTS</th>
<th>FU (MOS)</th>
<th>DATA SOURCE</th>
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<tbody>
<tr>
<td>Delalande et al., 2003</td>
<td>infant F</td>
<td>CPS &amp; gelastic</td>
<td>30/mo</td>
<td>no cog decline</td>
<td>NR</td>
<td>HH</td>
<td>3 covering entire HH</td>
<td>30</td>
<td>130 Hz, 90 μsec, 0.5 V; 185 Hz, 60 μsec, 0.1 V</td>
<td>increase in Sz freq, weight gain, headaches</td>
<td>12</td>
<td>NR</td>
<td>12</td>
<td>Kahane et al., 2003</td>
</tr>
<tr>
<td>Savard et al., 2003</td>
<td>2 yrs, M</td>
<td>gelastic, CPS w/ or w/o generalization &amp; drop attacks</td>
<td>daily</td>
<td>mod impairment, aggressive behavior</td>
<td>NR</td>
<td>HH &amp; it l in 1 int ANT, 1 HH</td>
<td>placement not specified</td>
<td>41</td>
<td>NR</td>
<td>no gelastic Szs, rare CPS, persistence of drop attacks</td>
<td>none</td>
<td>12</td>
<td></td>
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<tr>
<td>Khan et al., 2009</td>
<td>8 yrs, M</td>
<td>CPS</td>
<td>3/wk</td>
<td>cog decline</td>
<td>3</td>
<td>MTT 1 on rt side</td>
<td>16</td>
<td>140 Hz, 90 μsec, 1 min on, 3 V (2 min on, 1 min off)</td>
<td>Sz free</td>
<td>none</td>
<td>none</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khan et al., 2009</td>
<td>15 mos, F</td>
<td>CPS &amp; gelastic</td>
<td>daily</td>
<td>cog decline</td>
<td>4</td>
<td>MTT 1 on rt side</td>
<td>13</td>
<td>140 Hz, 90 μsec, 3.5 V (2 min on, 1 min off)</td>
<td>80% reduction in Sz freq</td>
<td>none</td>
<td>none</td>
<td>none</td>
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<td></td>
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<tr>
<td>Present case</td>
<td>13 yrs, F</td>
<td>gelastic &amp; CPS</td>
<td>10/mo</td>
<td>normal</td>
<td>4</td>
<td>HH</td>
<td>31</td>
<td>130 Hz, 90 μsec, 2.1 V</td>
<td>no sig reduction in Sz freq</td>
<td>none</td>
<td>none</td>
<td>18</td>
<td></td>
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</table>

* cog = cognitive; CPS = complex partial seizure; freq = frequency; FU = follow-up; mod = moderate; NR = not reported; sig = significant.
lies on the mammillo-thalamic-cortical pathway, could be considered as a target of DBS for the treatment of hamartoma-related seizures. Literature data showed that the hamartoma and the MTT are more effective targets than the ANT. Direct stimulation of the hamartoma permits a direct effect on the epileptogenic focus; the lower threshold of excitation and the smaller volume make the MTT suitable for epilepsy control. However, high-frequency stimulation of the ANT inhibits the spreading of interictal and ictal activity originating from hippocampal foci or from the hamartomas placed on the anterior hypothalamus; these data are supported by the work of Savard et al., who obtained good results by simultaneous stimulation of the ANT and their patient’s hamartoma. The patient was previously treated with callosotomy to control disabling seizures, with disappointing results. After combined stimulation of the 2 targets, disappearance of gelastic seizures and an impressive reduction of partial complex seizures were obtained, without any effects on seizures with falls.

After 18 months of stimulation, our patient had not obtained a significant reduction in overall seizure frequency; to establish the ideal parameter of stimulation and to avoid side effects due to hypothalamic stimulation, a longer follow-up period is mandatory. Moreover, the efficacy of unilateral stimulation (ipsilateral to the left electrode that recorded the interictal activity) rather than bilateral stimulation should be tested. According to Khan et al., investigation of stimulation parameters and a higher amplitude could be also considered.

The effect of neuromodulation on deep brain nuclei, exerted control by anterograde or antidromic stimulation or inhibition of the cortex, but no conclusive data on the ideal parameters for stimulation are known. The experience reported by Kahane et al. demonstrated seizure induction with frequency parameters ranging between 1 and 50 Hz. Velasco et al. reported on scalp-EEG synchronization followed by a recruiting response with a stimulation of 6–10 Hz to the centromedian thalamic nucleus, and spike wave complex recruiting response with a stimulation of 6–10 Hz to the hamartoma and the MTT are more effective targets than the ANT. Direct stimulation of the hamartoma permits a direct effect on the epileptogenic focus; the lower threshold of excitation and the smaller volume make the MTT suitable for epilepsy control. However, high-frequency stimulation of the ANT inhibits the spreading of interictal and ictal activity originating from hippocampal foci or from the hamartomas placed on the anterior hypothalamus; these data are supported by the work of Savard et al., who obtained good results by simultaneous stimulation of the ANT and their patient’s hamartoma. The patient was previously treated with callosotomy to control disabling seizures, with disappointing results. After combined stimulation of the 2 targets, disappearance of gelastic seizures and an impressive reduction of partial complex seizures were obtained, without any effects on seizures with falls.

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In conclusion, DBS is a safe and reversible procedure that could be suggested in difficult cases in which resective and disconnective surgery have a low rate of success and high morbidity. In addition, the use of DBS facilitates the collection of outstanding neurophysiological data. It could also be indicated when disconnective or resective surgery has failed, and could be considered as the first surgical option when the patient is neurologically and endocrinologically intact with a normal cognitive status.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. Author contributions to the study and manuscript preparation include the following. Conception and design: Marras. Acquisition of data: Deleo. Analysis and interpretation of data: Rizzi, Villani. Drafting the article: Marras. Critically revising the article: Rizzi, Villani, Messina, Cordella, Franzini. Reviewed final version of the manuscript and approved it for submission: Franzini. Statistical analysis: Deleo. Administrative/technical/material support: Rizzi, Messina. Study supervision: Marras, Villani.

Acknowledgments

The authors thank Suela Dyglieri, M.D., and EEG technologists Ambra Dominese and Sabrina Moretti for their important contributions during the intraoperative EEG monitoring. They are also grateful to Dr. Dyglieri for cultural contributions and to the Fondazione Paolo Zorzi for Neuroscience for support of their group and faith in their epilepsy program. Special thanks are extended to Enrica Pascarella and Fergal O’Reilly for kind assistance with the English translation of the manuscript.

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