YPOTHALAMIC hamartomas, originating from the tuber cinereum or mammillary bodies, are rare non-neoplastic lesions resembling gray matter, which are composed of hyperplastic neuronal tissue. They are often associated with early-onset gelastic seizures, thus configuring a well-recognized and usually severe case of childhood epilepsy syndrome. This syndrome is characterized by the early onset, often in the neonatal period, of brief, repetitive, attacks of uncontrollable laughter. These gelastic attacks progress as the patient ages, and other types of seizure, cognitive deterioration, and severe behavioral problems appear, frequently developing late in the first decade of life, together with drop-attacks and other clinical and EEG-demonstrated features of secondary generalized epilepsy. Patients with gelastic seizures and associated HH are often affected by the development of precocious puberty and a progressive mental decline.

Since Paillas, et al., reported successful seizure outcome after resection of the HH in some patients in 1969, surgical intervention in these lesions has been attempted with variable seizure outcomes; however, most epilepsy surgeons were reluctant to perform microsurgical resection of the perihypothalamic lesions because of the high risks of surgery including oculomotor palsy, hemiparesis, and visual field deficits. Recently, direct demonstration of the role of HH was provided by data obtained during stereo-EEG recordings. Moreover, Delalande and Fohlen have reported that only disconnection between the HH and the third ventricle floor by surgical and/or endoscopic means improved the refractory seizures without posing significant risk. Considering the pathogenetic role of HH in epileptogenesis, endoscopic disconnection of HH seems to provide an advantage over other procedures. We report the seizure outcome in four patients with HH-related intractable epilepsy who underwent endoscopic disconnection surgery between May 2001 and June 2002.

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Endoscopic disconnection for hypothalamic hamartoma with intractable seizure

Report of four cases

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Although intractable epilepsy associated with hypothalamic hamartoma (HH) can be controlled by microsurgical resection of the lesion, excision of deep-seated lesions is often associated with morbidity and mortality. Endoscopic disconnection is less invasive and seems to be well suited for this indication. The authors discuss the role of endoscopic-assisted surgery in the management of HH-induced seizures.

Four patients with HH-related intractable gelastic seizure underwent endoscopic disconnection surgery. Postoperatively, all patients exhibited improvement. Two patients became seizure free immediately after endoscopic disconnection surgery, one patient with a widespread seizure focus involving the motor strip continued to experience rare complex partial seizures but gelastic seizures ceased, and one experienced a reduced frequency of seizures but persistence of some generalized seizures. Three patients suffered postoperative disconnection-like syndrome, which continued 3 to 7 days and spontaneously disappeared.

The authors advocate the endoscopic disconnection surgery as a safe and effective treatment for HH-related epilepsy by blocking the spread of epileptic discharges from the lesion.

KEY WORDS • hypothalamic hamartoma • gelastic seizure • endoscopy • pediatric neurosurgery

HYPOTHALAMIC hamartomas, originating from the tuber cinereum or mammillary bodies, are rare non-neoplastic lesions resembling gray matter, which are composed of hyperplastic neuronal tissue. They are often associated with early-onset gelastic seizures, thus configuring a well-recognized and usually severe case of childhood epilepsy syndrome. This syndrome is characterized by the early onset, often in the neonatal period, of brief, repetitive, attacks of uncontrollable laughter. These gelastic attacks progress as the patient ages, and other types of seizure, cognitive deterioration, and severe behavioral problems appear, frequently developing late in the first decade of life, together with drop-attacks and other clinical and EEG-demonstrated features of secondary generalized epilepsy. Patients with gelastic seizures and associated HH are often affected by the development of precocious puberty and a progressive mental decline.

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Abbreviations used in this paper: CT = computerized tomography; EEG = electroencephalography; HH = hypothalamic hamartoma; MR = magnetic resonance; SPECT = single-photon emission CT.
Endoscopic disconnection for HH with intractable seizure

Clinical Material and Methods

We discuss four patients with medically refractory seizure associated with HH treated between May 2001 and June 2002. The HH were diagnosed and divided into four categories based on MR imaging findings focused on the relationship between HH and hypothalamus or the third ventricle (Fig. 1). Large hamartoma (>20 mm) was defined as giant HH (Type IV). Other small HHs (<20 mm) were classified as midline (Type I), lateral (Type II), and intraventricular (Type III) according to the relative locations of the HH to the third ventricle. The clinical features and radiological findings are summarized in Table 1.

Illustrative Case

Case 2

This 9-year-old girl presented with intractable seizure. She was born at term by normal vaginal delivery and there were no perinatal problems. She experienced episodes of abnormal uncontrolled laughter beginning at 1 year of age. These unprovoked episodes of pleasant laughter manifested five to 10 times per day. Her parents considered this brief laughterlike vocalization as normal until they observed brief atomic fits and generalized tonic–clonic seizure at age 3 years. Despite continuous medical treatment, she continued to experience seizures. At 9 years of age, she was transferred to our institution for treatment of the control of seizure.

Magnetic resonance imaging revealed a nonenhancing 18-mm-diameter sessile hypothalamic mass that protruded into the inferior third ventricle (Fig. 2). The mass was isointense in T1- and T2-weighted MR images, and was attached to the mammillary body and tuber cinereum. These findings were suggestive of a sessile HH. Moderate intellectual deterioration (Intelligence Quotient 69), and behavior problems were also present. We performed preoperative workup including EEG monitoring, MR imaging, positron emission tomography scanning, and interictal and ictal SPECT for localization of epileptic focus; however, the exact epileptogenic focus could not be localized. We inserted the depth electrode into the HH to identify its epileptic discharges and in this way confirmed the discharges preoperatively. The patient underwent endoscopic disconnection. When we advanced the telescope into the third ventricle, the HH was observed protruding from the floor and the lateral wall of the third ventricle. Using the monopolar electrical coagulator, we severed the lesion along the midline posteroinferior floor and protruding lateral wall of the third ventricle, between the hamartomas and the mammillary body (Fig. 3). Postoperative brain CT scanning revealed air density in the prepontine cistern, and MR imaging performed 7 days after the endoscopic procedure demonstrated the signal changes along the disconnection site between the mass and the hypothalamus. These findings indicated the complete disconnection between the HH and the hypothalamus. Intraoperative depth-EEG monitoring revealed the immediate disappearance of the epileptic discharges. We were able to obtain the small pieces of specimen, of which histological examination showed well-differentiated neurons, astrocytes, and oligodendrocytes that were exactly the same as the normal gray matter.

The patient exhibited no more gelastic seizures but continued to experience rare complex partial seizures. We suggested that persistence of some generalized seizures resulted from a widespread seizure focus involving the motor strip. She suffered disconnection-like syndrome, but the symptoms spontaneously resolved without causing neurological deficits by postoperative Day 4. Within 6 months of surgery, the family observed significant improvement in speech, behavior, and socialization despite the rare occurrence of generalized seizure.

| TABLE 1: Summary of clinical, neuroimaging, and seizure outcome data in four patients* |
|-----------------------------------------------|-----|-----|-----|-----|
| Case No. | Factor                        | 1   | 2   | 3   | 4   |
| sex     | age                           | F   | F   | M   | M   |
|         | at GS onset (mos)             | 6   | 12  | 10  | 6   |
|         | at CPS onset (yrs)            | 4   | 3   | 4   | 7   |
|         | at treatment (yrs)            | 16  | 9   | 6   | 29  |
|         | mental retardation (IQ)       | 70  | 69  | NA  | 60  |
|         | behavior abnormality          | +   | ++  | +   | ++  |
|         | precocious puberty            | no  | no  | no  | no  |
| HH features | size (mm)         | 12  | 18  | 14  | 25  |
|           | morphology                  | sessile | sessile | sessile | sessile |
|           | origin                      | both | both | MB  | MB  |
|           | hypothalamic displacement    | +   | +   | +   | +   |
|           | classification               | Type II | Type II | Type I | Type IV |
| follow up (mos) |                | 24  | 13  | 18  | 12  |
| seizure outcome |               | GS Class | 1   | I   | I   | II  |
|               | CPS Class                  | 1   | II  | I   | II  |

* Both = mammillary body and tuber cinereum; CPS = complex partial seizure; GS = gelastic seizure; IQ = intelligence quotient; MB = mammillary body, TC = tuber cinereum; NA = not available, + = mild, ++ = moderate, +++ = severe; − = none.

Fig. 1. Classification of sessile HH (modified from that proposed by Delalande and Fohlen). The HHs were divided into four categories based on MR imaging findings demonstrating the relationship between the hamartoma and hypothalamus or the third ventricle. A large hamartoma (>20 mm) was defined as a giant HH (Type IV). Other small HHs (<20 mm) were classified as midline (Type I), lateral (Type II), and intraventricular (Type III), according to their relative location to the third ventricle.
Summary of Overall Patient Data

All patients included in our report suffered severe drug-resistant epilepsy as a primary symptom, and there were no cases of precocious puberty. The patient in Case 2 had a history of unsuccessful gamma knife surgery. The mean age at the time of the endoscopic procedure was 15 years (range 6–29 years); the age at the time of gelastic seizure onset ranged from 6 to 12 months (mean 8.5 months). The gelastic seizures were characterized by the early onset of brief, repetitive, typical attacks of uncontrollable laughter. All patients experienced several types of seizures in addition to the gelastic seizures. Complex partial seizures occurred 2 to 7 years (mean 3.8 years) after the first gelastic seizure attack and were characterized by behavioral arrest associated with bilateral motor manifestations. The seizure frequency ranged from three episodes per week to more than 10 episodes a day for gelastic seizures and from one episode a month to two episodes per day for generalized seizures. These seizures were resistant to two or more antiepileptic drugs. The patients exhibited moderate-to-severe mental retardation and behavior abnormalities.

To identify the epileptic focus, we performed scalp EEG, ictal and interictal SPECT, and video-EEG recording in which a depth electrode was directly inserted into the HH. In the latter case, the depth electrode was retained within the tumor after surgery. We performed endoscopic disconnection to control the seizure. Seizure outcome was scored according to Engel classification during a mean follow-up period of 16.8 months (range 12–24 months).

Endoscopic Disconnection Between Hypothalamus and Hamartoma

Our instrumentation for endoscopic disconnection consisted of a 30° Hopkins pediatric telescope (outside diameter 2.7 mm), a sheath for the telescope (outside diameter 3.8 mm), a stylet, a monopolar electric coagulator or an Nd-Yag laser system, a fiberoptic light guide, an Xe light source, and an endovision system. An endoscopic procedure was performed after induction of general anesthesia. In the standard procedure, a burr hole was made 1 cm in front of the coronal suture and 2 to 3 cm lateral to the midline. The right lateral ventricle was tapped using a ventricular catheter inserted through the burr hole. A peel-away catheter was then replaced via the tract. The telescope with the sheath was then advanced into the lateral ventricle through the peelaway catheter. When we advanced the telescope through the foramen, we could see the HH protruding from the floor and the lateral wall of the third ventricle. We could easily determine the confines of the protruding hamartoma and the normal hypothalamus by direct visualization; however, we had difficulty determining the tumor limits in one case. The site for endoscopic disconnection was along the midline posteroinferior floor and protruding lateral wall of the third ventricle between the hamartomas and the mammillary body. The depth of disconnection was determined by examining the preoperative T1- and T2-weighted coronal MR images. For disconnection, the monopolar electric coagulator or the fiberoptic electrode of the Nd-Yag laser system was advanced through the working channel of the sheath. The monopolar electric coagulator was easily capable of severing or coagulating the hamartoma under direct visualization. The complete disconnection between the HH and the hypothalamus could be confirmed by observing air density along disconnection site on postoperative brain CT scans or signal changes on T1-weighted and T2-weighted coronal MR image.

Results

Intrinsic Epileptogenicity of HH

Interictal scalp EEG demonstrated intermittent brief spike and wave complexes with slow background activities, and ictal scalp EEG revealed a rhythmic buildup of poorly localized low-voltage fast β activity lasting 4 to 5 seconds. Although these findings indicated the existence of mild or moderate diffuse cerebral dysfunction, they were insufficient to localize the exact epileptogenic focus. Other studies including ictal and interictal SPECT and MR imaging were not useful in localizing the epileptic focus. We stereotactically inserted depth electrodes into the HH to identify the epileptic discharges from the HH in three patients (Cases 2–4). These depth electrodes were maintained within the HH during and until 1 week after the endoscopic procedures. We could confirm the HH-induced epileptic discharges by using preoperative depth electrode monitoring and observe the immediate disap-
Endoscopic disconnection for HH with intractable seizure

Seizure Outcome and Complications

All patients exhibited improvement. Two patients (Cases 1 and 3) became seizure free immediately after endoscopic disconnection. One patient with a widespread seizure focus that involved the motor strip (Case 2) continued to experience rare complex partial seizures but not gelastic seizure. One patient with Type IV HH (Case 4) exhibited only improvement, with reductions in the frequency of seizures but persistence of some generalized seizures; his follow-up MR images demonstrated incomplete disconnection of the HH. There were no deaths and deficits related to endoscopic procedures. In three cases we observed postoperative disconnection-like syndrome including mental dullness, verbal anosmia, unilateral tactile anoma, unilateral constructional apraxia, and lack of somesthetic transfer. This disconnection-like syndrome continued 3 to 7 days after endoscopic disconnection but spontaneously disappeared without neurological deficits. Their families reported a dramatic improvement in behavior in the 2nd postoperative month in all patients.

Discussion

Hypothalamic hamartomas are rare nonneoplastic malformations that originate from the area around the tuber cinereum or mammillary bodies. These lesions are often associated with early-onset gelastic seizures. Gelastic seizure beginning in infancy and progressing with age causes several types of secondary generalized seizures and leads to cognitive deterioration and severe behavioral problems. These seizures are difficult to control medically.

The origin and pathophysiology of the epileptic attacks in HH are obscure. Cascino, et al., failed to identify a clear epileptogenic cortical area in their study when performing intracranial EEG monitoring and pathological examination of resected cortex sample thought to be

Fig. 3. A and B: Endoscopic views of the third ventricle floor. When we advanced the telescope into the third ventricle, the HH was observed protruding from the floor and the lateral wall of the third ventricle. The site for endoscopic disconnection (asterisk in B) was along the midline posteroinferior floor and protruding lateral wall of the third ventricle between the hamartomas and the mammillary body (MB). The monopolar electrical coagulator (ME) easily severed or coagulated the hamartoma under direct visualization. IR = infundibulum recess.
epileptogenic. In a recent spectroscopy study on the temporal lobe the authors were also unable to identify an epileptic focus for the gelastic seizures. In 1969, Paillas, et al., were the first to suggest the role of HH in the genesis of seizures, demonstrating that seizure improved after resection of HH. In recent reports involving stereo-EEG recording or SPECT, it was asserted that HH is directly responsible for seizures through proper epileptogenicity. The relationship between HH and seizure, however, remains obscure. Several hypotheses have been posed. The first suggestion is that the proximity of the HH to the hypothalamus causes the stimulation of diencephalons and/or the limbic system. This assertion is supported by certain obvious facts such as the observation that sessile HH is more related to epilepsy than pedunculated HH, and that the displacement of the hypothalamus by HH and the size of the tumor may be closely related to epilepsy. On the basis of this suggestion, many reporters of surgically treated cases pointed out that total or near-total resection was very important to control the seizures. The results in most cases of HH associated with seizures including ours, however, indicate that total resection of these sessile lesions is extremely difficult without significant surgical risks because precise delineation of the HH is difficult. In fact, microsurgical resection in this critical area may be related to a high risk of oculomotor palsy, hemiparesis, visual field deficits, central diabetes insipidus, and nonreversible hyperphagia. Most neurosurgeons are, therefore, still reluctant to undertake surgery in the case of perihypothalamic lesions.

In the second hypothesis, seizure mechanism is attributed to the HH’s being intrinsically epileptogenic, with the epileptic discharges spread from it. If we had accepted this hypothesis, total resection of the HH would not have been mandatory. The HH-related seizures could be controlled by blocking the seizure propagation from epileptogenic HH by performing a simple disconnection procedure, regardless of the treatment modality. In 1997, Kuzniecky and colleagues confirmed the intrinsic epileptogenesis of HH by placing a depth electrode; they successfully treated frequent gelastic seizures in three patients with HH by performing stereotactic radiofrequency lesioning. In 2003, Delalande and Fohlen reported successful seizure-related outcomes in 14 patients who underwent open surgical disconnections, although there were two cases in which complications occurred. We confirmed this hypothesis by placing a depth electrode in the HH. In three patients who underwent endoscopic disconnection, we inserted depth electrodes and directly recorded the HH-related epileptic discharges. We maintained the depth electrodes within the HH during and for 1 week after the endoscopic procedures. We observed the immediate disappearance of the epileptic discharges on intraoperative EEG monitoring via the depth electrode during endoscopic disconnection. Intraoperative and postoperative EEG monitoring via the depth electrode was valuable in allowing decisions concerning the depth of the endoscopic disconnection. We expected that epileptic discharge would continue without its propagation if the HH were intrinsically epileptogenic; however, we observed no epileptic discharges after surgery. We propose that the neuronal function of HH is temporarily or permanently lost because of the thermal effects of the electrical coagulation during endoscopic disconnection. We also believe the postoperative disconnection-like syndrome may result from the thermal damages of the hypothalamus due to the electrical coagulation. Although disconnection-like syndrome occurred in all patients, it spontaneously resolved without causing neurological deficits 3 to 7 days postoperatively. In the same manner, the HH’s lost neuronal functions may recover approximately 1 week after surgery and create the epileptic discharges. Unfortunately, we were unable to confirm whether the loss of neuronal function was temporary or permanent because EEG monitoring was not performed after 1 week postoperatively.

In this study, we propose a new classification of sessile HHs based on topographical and clinical data. This system should help to classify the various treatment methods and the surgical risks into four subgroups. In our preliminary experience involving this endoscopic procedure, Types I and II HH could be separated from the hypothalamus without causing significant surgery-related risks; this was because they could be easily identified under direct visualization and because they are connected to the hypothalamus by very thin tissues. Although we did not encounter Type III HH, we believe these lesions can also be resected for the same reasons. Type IV HH, however, was difficult to treat by endoscopic disconnection. As analysis of
our data indicated, a Type IV HH has a broad base connecting to the hypothalamus, which makes complete disconnection difficult and, during the electrical coagulation for disconnection, damages the hypothalamus terminally. Hypothalamic hamartoma is a very rare disease entity, and our series was too small to allow valid conclusions to be drawn based on the data. We showed, however, that the endoscopic disconnection was a realistic alternative in certain cases involving Types I, II, or III HH associated with gelastic epilepsy and behavioral disorders. Type IV HH was very hard to treat using only endoscopic disconnection; additional treatment such as radiosurgery, repeated endoscopic surgery, and open surgery should be considered in such cases.

Conclusions

We confirmed that HH is intrinsically epileptogenic and, using the depth electrode placed in the HH, that the epileptic discharges spread from the lesion. Therefore, we assert that blocking the cause of seizure by performing endoscopic disconnection may control HH-related seizures. Endoscopic disconnection is safe and effective, although resection or radiosurgery is a valuable treatment modality for intractable HH-related gelastic seizure.

References


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