The intrahypothalamic subtype of hypothalamic hamartoma (HH) is usually associated with refractory epilepsy, cognitive impairment, and organic behavioral disturbance. It is often a devastating disorder for both patient and family. The gelastic (laughing) seizure is the hallmark seizure type. However, multiple other seizure types can often develop during the course of the disease, and are typically refractory to antiepilepsy drugs (AEDs). Previously it was uncertain if HH tissue was responsible for seizure genesis or whether resection of the HH would result in improvement of the seizures. Recently both of these questions have been answered in the affirmative. Surgical resection using a transcallosal, interforuncial approach has recently been shown to be efficacious and generally safe for the treatment of the refractory seizures. However, even more recently, we have been performing the majority of HH surgical resection by using an endoscopic technique with a transventricular approach. This article presents the details of the operative technique and discusses preliminary outcome data, particularly with comparison to the transcallosal technique. Using an endoscope holder with micromanipulator facilitates endoscopic resection. Linking the endoscope to a system of frameless stereotaxis is essential for successful resection. Forty-four patients age 8 months to 44 years have undergone endoscopic resection. The ideal candidate for endoscopic removal has a hamartoma completely or nearly completely involving one wall of the third ventricle and is 1 cm or less in greatest diameter. Because it is essential to be able to visualize the lesion within the third ventricle for resection, there must be at least 6 mm of space between the top of the lesion and the roof of the third ventricle. Patients with intractable epilepsy caused by HH can be rendered seizure free or show marked improvement in seizure frequency by surgical removal, surgical disconnection, or radiosurgical ablation of the lesion. Which of these options should be recommended for an individual patient is not yet clear. One of the options involves resection or disconnection of the HH with a transventricular endoscopic approach. In selected patients, endoscopic resection of HH is effective in the treatment of intractable epilepsy, with lower complication rates and shorter hospital stays than transcallosal resection.

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Hypothalamic hamartomas (HHs) are rare congenital tumors of the inferior hypothalamus. Various symptoms have been associated with intrahypothalamic (sessile) form of HH, including refractory epilepsy, often with multiple seizure types, central precocious puberty, intellectual impairment, and behavioral problems.

Although most patients tend to have multiple seizure types (mixed seizure disorder), the most characteristic seizure type is the gelastic (or laughing) seizure. Gelastic seizures often are the earliest seizure type manifested by patients with HH. However, at times, the brief ictal phase of laughter and/or smile is often ignored or disregarded by primary care physicians, and the diagnosis is not made until many months or
even years later (often only when other seizure types begin to occur). Gelastic seizures may have some degree of the appearance of fear or anxiety involving the patient. The sessile or intrahypothalamic type in which the HH is enveloped by the hypothalamus is thought to be the most strongly associated with gelastic seizures because of their juxtaposition to the hypothalamus and its associated central connections.5,5

Multiple other seizure types eventually occur in most patients with HH, and, although nearly all seizure types have been seen, they typically include tonic, tonic-clonic, and complex partial seizures.3,4 The natural history and basic mechanisms underlying the evolution and sites of onset of seizures associated with HH is complex and is reviewed by Harvey and Freeman in an article in this issue. However, summarized briefly, the current model includes the following elements: (1) the HH is intrinsically epileptogenic, and gelastic seizures arise, perhaps exclusively, from the HH; (2) other seizure types may begin as gelastic seizures or as subclinical seizure discharges within the HH and spread secondarily to other brain structures, resulting in seizures that can appear either partial or generalized; (3) the HH (or the seizures that arise from the HH) can influence neocortical regions by a poorly understood process of secondary epileptogenesis so that these regions can generate seizures independent of activity in the HH; and (4) for some, this process of secondary epileptogenesis can be reversed (the “running down” phenomenon) after successful resection of the HH. In others, the process of secondary epileptogenesis is permanent, and seizures may continue to arise from neocortical structures despite “successful” resection of the HH. The basic cellular and molecular mechanisms responsible for these features are poorly understood.

Treatment of the Seizures and Epilepsy
Gelastic and other seizure types associated with HH are notoriously difficult to treat with traditional or even the newer antiepileptic drugs (AEDs). Despite high doses of multiple AEDs, seizure freedom or even good seizure control is rarely achieved in this group of patients. Accordingly, various other therapies have been tried with variable success in treating the seizures, including vagal nerve stimulation, gamma knife radiotherapy, stereotactic destruction of the lesion through radiofrequency thermoablation, and even gonadotropin-releasing hormone analog therapy.9,17

Until relatively recently, it had been believed that the HH was not clearly responsible for the seizures, and, even when physicians began to realize otherwise, it was believed that the HH was inaccessible and too difficult for resective surgery. There is now increasing evidence that the HHs can indeed be effectively treated with a variety of neurosurgical approaches, with often complete seizure control or at least dramatically improved seizure control and quality of life.18 Options include a transcallosal interforniceal approach, pterional approach, orbitozygomatic approach, and transventricular endoscopic approach. In our previous experience, the transcallosal approach offered the best chance of seizure freedom or good seizure control even when there was incomplete resection of the HH. This may be because of more efficient disruption of the central connections of the HH to other cortical or subcortical brain regions as a result of approaching the HH from a superior trajectory. Our published data in 26 patients undergoing HH resection with the transcallosal interforniceal approach showed a seizure-free rate of 54% and that overall 88% of patients had at least a 90% reduction in seizure frequency.19 These figures are very similar to the Australian series20 as reviewed by Rosenfeld and Feiz-Erfan in this issue.

Within our more recent experience, over the last 2 years or so, the majority of HH patients (more than 50) have been operated on by the transventricular endoscopic resection. Preliminary results of this patient series are updated here. Detailed outcome findings in those patients with at least 1 year of postoperative follow-up will be reported in a future peer-reviewed submission. Recently, a publication by Pro-caccini and coworkers21 described a series of HH cases undergoing frameless stereotactic endoscopic disconnection. However, their data are a little difficult to interpret because from their 26 patients who underwent endoscopic resection, 16 had at least 2 procedures including repeat endoscopic resection, pterional resection, or gamma knife. In addition, follow-up was on average just under 18 months but as short as 1 month. Nevertheless, the outcome results were promising with a seizure-free rate of an overall 33 patients (undergoing various operative procedures) of 48.5% and a further 48.5% with significant seizure amelioration (Engel classes 2 and 3).21

Patient Selection
A total of 44 patients with HH and refractory epilepsy underwent transventricular endoscopic resection of HH lesions between January 2004 and April 2005. The mean age was 15.0 years, the median age was 10.0 years, and the range was 0.7 to 55 years. Earlier results on this cohort of patients have been reported.22 Subsequent to informed consent, the patients were followed with prospective entry into a proprietary research database under protocols approved by the institutional review board of the Barrow Neurological Institute of St. Joseph’s Hospital and Medical Center. Informed consent for specific surgical procedure was also obtained.

All patients had refractory epilepsy as defined by failing a medical treatment regimen consisting of at least 3 AEDs. All patients had a history of gelastic seizures at some point during their clinical course, many which began as early as the first week of life. As patients reached early childhood and adolescence, their seizure disorder tended to worsen and develop into mixed epilepsy with multiple seizure types (with encephalopathy). All patients had some difficulty with cognitive function, ranging from mild difficulties with short-term memory to severe mental retardation and uncontrollable rage attacks.

Eleven patients had undergone previous surgical procedures for their HH, including previous attempts at subtotal
resection (3 patients), gamma knife radiosurgery (3 patients), stereotactic radiofrequency thermoablation (1 patient), and vagal nerve stimulation (6 patients).

Initially, in this chronological series, endoscopic disconnection was considered sufficient to treat HH in most patients, but the lack of a clear definition of what is meant to disconnect these lesions became increasingly apparent. Consequently, patients lacking an interface with the hypothalamus within the third ventricle and with HH lesions filling the third ventricle were not considered as candidates for transventricular endoscopic resection. The instruments used to resect or disconnect the HH under direct vision require that the distance from the foramen of Monro to the superior surface of the HH mass be at least 6 mm. HH lesions whose base of attachment projects under the optic tract are also difficult to disconnect or remove using endoscopic surgery alone.

Method (Surgical Technique)

The initial endoscopic HH resection in this series was performed on a 30-year-old man because we found that, particularly in adult patients, the transcallosal technique can be more challenging because of fusion of the leaves of the septum pellucidum that appears to be much more likely with increasing age. Figures 1 to 3 show his pre- and postoperative coronal brain magnetic resonance imaging (MRI) scans. His left-sided attached HH indicated that the endoscopic approach should be from the right via the right lateral ventricle. (This patient has now been completely seizure free for over 2 years, without complications.)

All cases have been performed under general anesthesia in a supine, head-up position. The head is fixed in a slightly flexed position in the Mayfield Frame (Codman Inc, Raynham, MA) or, for children younger than 18 months of age, in a gel-based modification. The ideal HH for neuroendoscopic resection or disconnection is attached to one wall of the hypothalamus, rather than having bilateral attachment (Fig 1). All patients had small (normal-sized) ventricles.

A 3-cm parasagittal incision is placed immediately anterior to the coronal suture and 2 cm off midline. The site of the bur hole is chosen to allow a direct path through the foramen of

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**Figure 1** Coronal preoperative, T2-weighted MRI brain scan of our first patient who was operated on by endoscopic resection showing the slightly left-sided hypothalamic hamartoma located on the floor of the third ventricle with 2 normal temporal lobes.

**Figure 2** Postoperative coronal views showing the resected HH and endoscopic shunt tract. Because the HH was attached on the left, the approach was from the right side, into the lateral ventricle through the foramen of Monro to the floor of the third ventricle.
Monro to the interface of the hamartoma. Consequently, the point of insertion is usually about 3 cm lateral to the sagittal suture and about 1 cm anterior to the coronal suture. The procedure is performed with frameless stereotaxy (Stealth Frameless Stereotaxis; Medtronic Corp, Minneapolis, MN). A Suretrac (Medtronic Corp; Minneapolis, MN) tracking device was inserted into the trocar of a 20-F peelaway sheath. This device was registered to the Stealth unit (StealthStation Treon; Medtronic Navigation, Louisville, CO) so that the ventricle could be cannulated accurately. After the ventricle is cannulated, the peelaway sheath is opened and affixed to the scalp by using staples. Using frameless stereotactic guidance, a 30° endoscope (Aesculap, Tutlingen, Germany) is placed into the lateral ventricle. The Unitract endoscope holder (Aesculap) is the preferred choice to control the position of the endoscope. A Neuropilot (Aesculap) attached to the Unitract endoscope holder allows micromotion of the endoscope by turning wheels in 3 dimensions. The trajectory can be changed by releasing the rigid fixation of the endoscope by the Unitract system. Such changes can be achieved without disconnecting the endoscope-scope holder unit. A passive reference arch attached to the endoscope provides neuronavigational control of the tip of the endoscope throughout the procedure (Fig 4).

After entry into the lateral ventricle with the endoscope, the choroid plexus is followed to the foramen of Monro. The endoscope is advanced to the foramen of Monro in a trajectory that approaches the location of the mammillary bodies. At this point, the bulging hamartoma can be identified clearly, and the boundary between the hamartoma and the third ventricle wall can be readily seen. The initial disconnection is directed by the anatomic interface seen on MRI and defined by the frameless stereotaxis. Depending on the individual anatomy of a hamartoma, this interface is dissected until the pial surface or the ependymal surface of the floor of the third ventricle is identified.

The endoscopic micropituitary rongeur is introduced through a working channel. The interface between the hypothalamus and hamartoma is dissected circumferentially in a piecemeal fashion, the center of the hamartoma is debulked, and the endoscopic tools are removed. A ventriculostomy is placed on the lateral ventricle, and the wound was closed in a standard fashion.

The average operating time is very different for the transventricular endoscopic resection in comparison to the transcallosal interforniceal resection of the HH lesions. The endoscopic operation averages between 60 to 90 minutes in duration, whereas the average transcallosal procedure takes between 5 to 6 hours. Endoscopic resection of HH is an excellent example of minimally invasive neurosurgery. Rather than a craniotomy that crosses the midline (and the superior sagittal sinus) twice, and that requires the retraction of the hemispheres, and eventually the columns of the fornix bilaterally, the endoscopic resection is performed through a single bur hole and without brain retraction. The patient is usually awake...
within an hour after completion of the procedure and ready to leave the hospital within 4 days.

**Complications**

There were no deaths in this series.22 One patient was lost to follow-up after hospital discharge. Complications occurred in 11 patients (25%) but resolved within 3 months in all but 3 patients (6.8%). After surgery, 6 patients had difficulties with short-term memory, transient with complete recovery in 3, and persisting more than 3 months in 3 patients. Five patients gained more than 10% of their body weight, but the gain stabilized and improved within 3 months in all 5. One patient experienced unilateral injury to the internal capsule during endoscope manipulation, resulting in significant hemiparesis, which improved slowly over a year.

In 11 patients (25% of study group), postoperative diffusion-weighted MRI showed small thalamic lesions, usually unilateral, that presumably indicated infarctions related to a posterior cerebral artery perforator or damage to venous structures in the interpeduncular cistern. Intraoperatively, the pial surface of the floor of the third ventricle in these cases was perforated without significant bleeding. Of these 11 patients, 3 had contralateral hemiparesis in the immediate postoperative period consistent with their MRI findings. One of these 3 is the patient noted to have traumatic injury to the internal capsule, noted earlier. In the other 2 patients (of the 3 with immediate postoperative hemiparesis), the motor deficit resolved completely within a week of surgery. The remaining 8 patients were entirely asymptomatic with respect to these small thalamic infarcts. In our series, most endoscopic or transcallosal procedures penetrated the interpeduncular cistern during resection. Depending on the patient’s anatomy and lesion, a functional disconnection or removal is pursued.

The outcome data related to return to baseline function, improvement in behavior, and control of seizures between the transcallosal and endoscopic resection groups are similar at the 6-month postoperative time point. However, the immediate postoperative course for the transcallosal and endoscopic resection groups differ significantly (see later). The endoscopic cases are now carefully selected and are somewhat less complex cases, but are back to baseline within a few days of surgery. If the endoscopic resection is a viable option because of anatomic criteria, it is our preferred approach at this time. The transcallosal interfornical approach to the HH becomes more challenging with increasing age of the patient because of the increasing likelihood of adhesion and difficulty of separation of the leaves of the septum pellucidum. This is a particularly important operative issue in adult patients.

**Preliminary Results**

**(Comparison With the Transcallosal Series)**

Preliminary analysis of outcome was performed with comparison between the transventricular endoscopic HH resection group (n = 37 patients with at least 12 months of available postoperative follow-up) and our previously published cohort of HH patients undergoing transcaldosal interfornical resection (n = 26).19

Overall, the likelihood of 100% seizure control did not differ significantly between the endoscopic (49%) and the transcallosal (54%) HH cohorts (P = .51, χ² test). For those who were not 100% seizure free, an improvement of at least 90% in seizure frequency was observed in 21% of the endoscopic patients and in 35% of the transcallosal cases. Combining the patients with complete seizure control and those with at least 90% improvement in seizure frequency to define surgical “success,” 70% of patients in the endoscopic group were successful in comparison to 89% of the transcallosal group.

There was, however, a clinically and statistically significant difference between the 2 groups with respect to the duration of the postoperative hospital stay, clearly favoring the endoscopic group of patients. The mean number of postoperative hospital days required before discharge in the transcallosal group of patients was 7.7 days (standard deviation = 4.6 days) and in the transventricular endoscopic group 4.5 days (standard deviation = 1.3 days, P = .0006 by Satterthwaite t test).

Currently, we favor performing the endoscopic resection in the majority of our HH cases, although every case is reviewed on an individual basis and the surgical approach is tailored to the patient’s unique circumstances, primarily based on imaging and to a lesser degree on age at time of surgery. If the HH tumor is large and attached bilaterally to the hypothalamus, transcallosal resection may be performed. If the lesion is pedunculated with an inferior, horizontal plane of attachment below the floor of the third ventricle, an orbitozygomatic approach may be used (3 patients in the Barrow HH series to date). Lastly, for patients with particularly large lesions with bilateral and complex planes of attachment, we have performed HH resection/disconnection through a simultaneous transventricular endoscopic and eyebrow craniotomy approach with 2 neurosurgeons performing the operation (the “combined approach”). Thus far, 3 patients in the Barrow HH series have been treated with this surgical technique.

**Discussion**

Multiple surgical approaches and techniques have been used and described in the resection of HH including subfrontal, transsylvian, subtemporal, frontotemporal, pterional craniotomy, interhemispheric and translamina terminalis, and epidural subtentoropergial approaches.19,23-37 Unfortunately, many of these techniques are associated with high complication rates including capsular and thalamic infarcts (with associated hemiparesis), third nerve palsies, and memory loss but equally importantly often do not result in adequate resection of the tumor with persisting seizure activity. Until recently, HH resection via the transcallosal-interfornical route have had clearly the largest series of patients described who were treated successfully.4,19,20 The most significant residual complication has been short term memory loss.
(usually transient) in a few patients. Another recent series of patients described patients who underwent many different and usually combined surgical procedures including frameless, stereotactic endoscopic resection.\(^2\) Transventricular endoscopic resection is an additional option for selected patients. Our experience, reported in preliminary fashion here, in a sizeable patient cohort, supports the premise that endoscopic resection may be as effective as transcallosal resection, and, at least in the short term, is more easily tolerated by the patient with more rapid postoperative recovery to baseline. Surgical resection of intraventricular masses has the potential to be a perfect application for the surgical robot as a scope holder. This device may lead to more precise and smooth minimal movements of the scope for safer and more complete resection. Such a device is not yet available for intracranial neuroendoscopy in the United States.

In summary, HH is a rare but potentially devastating congenital malformation resulting in trademark gelastic seizures but also eventually in the development of other seizure types, all typically resistant to medical therapies. In addition, severe cognitive, behavioral, and endocrinologic complications are often associated. Transventricular endoscopic resection of this tumor is effective, largely safe, and at present may be the best form of treatment for HH in appropriate patients, with the shortest recovery time. In closing, it should be noted the most attractive candidates for HH resection by an endoscopic approach are also those that are most attractive for treatment with gamma knife radiosurgery (that is to say, relatively small and unilateral and type II by the Delalande classification).\(^{38,39}\) The relative merits of these 2 approaches require further study, although, ultimately, the decision on the part of the patient, family, and treating physicians will be based on weighing the factors that appear to be associated with each including more immediate response and greater likelihood of success but significantly higher risk of complications with endoscopic resection and the delayed effectiveness but superior risk profile associated with gamma knife. The difference in the time to achieve an effective therapeutic response for each approach is an important consideration, particularly for those patients who have had exclusively gelastic seizures, but have now begun to develop multiple, poorly controlled seizure types, which is often the time point for neurobehavioral deterioration as well.\(^{5,7,8}\)

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