

Surgical approaches to hypothalamic hamartomas

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Object. Hypothalamic hamartomas (HHs) are devastating lesions causing refractory epilepsy, rage attacks, social ineptitude, and precocious puberty. Microsurgical and/or endoscopic resection offers an excellent risk/benefit profile for cure or improvement of epilepsy.

Methods. The authors reviewed a prospective database maintained during the first 7 years of the Barrow Hypothalamic Hamartoma program. They describe and illustrate their surgical methods, and they review data from several previous publications regarding surgical outcome.

Results. To date, the authors have performed surgery in 165 patients for symptomatic HHs. Patients underwent an endoscopic, transcallosal, or skull base approach, or multiple approaches. Twenty-six patients (15.8%) required more than 1 treatment for their HH.

Conclusions. Microsurgical and endoscopic resection of symptomatic HHs are technically demanding but can be performed safely with excellent results and an acceptable risk profile. Meticulous attention to the subtleties of surgical management helps optimize outcomes. (DOI: 10.3171/2010.11.FOCUS10250)

KEY WORDS • hypothalamic hamartoma • endoscope • microsurgery • epilepsy

HYPOTHALAMIC hamartomas are rare CNS nonneoplastic lesions composed of hyperplastic neural tissue^{3,24} associated with 2 patterns of presentation. The Delalande classification classifies HHs based on size, and amount of and laterality of attachment to the hypothalamus.⁴ Children with HHs that are significantly attached to and involved with the hypothalamus become symptomatic with gelastic seizures (Delalande Types II, III, and IV). These lesions are usually resistant to medication and if left untreated devolve into more sinister epileptic patterns as the child grows.^{21,23} Furthermore, children with these lesions may develop problems with social interaction, including frequent rage attacks. In contrast, Delalande Type I HH can cause central precocious puberty and may be treated medically with excellent results.⁴ This type of HH seldom manifests with epilepsy or behavioral problems, and microsurgical excision tends to be curative.^{5,14}

The Barrow Hypothalamic Hamartoma Program was established late in 2003. Thus far, we have treated many patients with HH.^{1,3,5–10,13,15–21,23,25} The goal of this manuscript is to describe, in a single, free, online, easily

Abbreviations used in this paper: ACA = anterior cerebral artery; GKS = Gamma Knife surgery; HH = hypothalamic hamartoma.

accessible publication, the current methods of resection and to share pitfalls and pearls that we have learned during the process. The approaches used can be classified as endoscopic, transcallosal, or skull base. We also review data previously published by our group on the outcomes and complications associated with this challenging group of patients. This project is ongoing and continues to accrue data.

Methods

Between late 2003 and late 2010, the Barrow Hypothalamic Hamartoma Program has treated 165 patients with a symptomatic HH. The patients have come from many states and countries. The program operates under the approval of the institutional review board of St. Joseph's Hospital and Medical Center, Phoenix, Arizona. A team of physicians, including neurosurgeons, epileptologists, neuroradiologists, and endocrinologists, reviews each case. Each patient is also thoroughly reviewed by each specialty, and their cases are presented at the monthly HH conference to obtain a consensus on the appropriate treatment. Data from each patient are cataloged in a prospective fashion, and portions have been reported in several publications.^{1–3,5–10,15,17–21,23,25} In especially instruc-

tive or unusual cases, pre- and postoperative imaging studies, surgical videos, intraoperative photographs, and other appropriate data are also cataloged. We reviewed selective cases treated at different times to evaluate our methods, to share surgical pearls and surgical pitfalls, and to obtain an understanding of how our surgical approaches have evolved over time.

Operative Techniques

We have used 3 approaches to address HHs: transventricular endoscopic, transcallosal, and skull base approaches. No single approach is the best approach or is appropriate in all cases. Adequate treatment requires individualization of the approach based on a patient's age and condition, on the anatomy of the HH, and on the surgeon's experience. It is becoming increasingly clear that a 1-stage approach to all HHs is probably inappropriate. We often plan a staged approach depending on the extent of resection or disconnection achieved with the initial treatment, the patient's symptomatic response to the initial treatment, and the willingness of the patient and family to undergo further treatment. Stereotactic radiosurgery, either as a stand-alone treatment or treatment for postoperative residual HH, is now included in the treatment paradigm for appropriate patients.²

Endoscopic Resection

Endoscopic resection is preferred as the stand-alone surgical treatment for small Type II HHs and as a stage in the treatment of small Type III HHs.

Stereotactic guidance is required in these cases for 3 reasons. First, the entry point is chosen based on using the trajectory views provided by the stereotactic software. Second, the trajectory of resection is determined by tracking the end of the endoscope and again, using the trajectory views to best estimate the course of the HH/normal hypothalamus interface (Fig. 1C). Third, endoscopic entry into a small ventricle is often aided by stereotaxy. The entry point is determined by finding the point on the scalp that is intersected by a line drawn from the anterior edge of the side of HH attachment to the hypothalamus and the anterior edge of the contralateral Monro foramen. This is easily done using the trajectory views provided by the stereotactic software. Thus, a right-sided HH will be approached from the patient's left side.

Once the entry point is chosen, a generous bur hole is made, and the dura is coagulated and opened. The pia is also coagulated and opened. We then place a peel-away sheath into the brain along the appropriate trajectory and stop just short of the ventricle. Most patients do not have hydrocephalus, and blindly placing a sheath in a small ventricle is challenging. Once the sheath is placed, we use a stereotactic-tracked 30° endoscope and endoscopic visualization to advance the tip of the scope into the ventricle.

Once the ventricle is entered, gentle irrigation is infused to induce mild ventriculomegaly and the sheath is advanced over the endoscope until it is just inside the lateral ventricle. Placement of the sheath in the ventricle relieves the ventriculomegaly and leaves a small space within which to work. The choroid plexus and anatomy of

the ventricular venous system guide the endoscope through the Monro foramen and into the third ventricle. Care must be exercised to avoid forcefully impinging the fornix at the anterior margin of the foramen. While the tip of the endoscope is in the third ventricle, the fornix is not visible. The entry point is chosen as described above because the fornix will not tolerate anterior "windshield wiping" of the endoscope. Gentle posterior "windshield wiping" movements are better tolerated but should be minimized.

Once the third ventricle has been accessed, gentle irrigation will separate the walls enough to provide a clear view of the anterior and posterior margins of attachment. The endoscope is secured in place using a robotic manipulator arm (Fig. 1B). We then obtain microelectrode recordings in the HH for research purposes.¹⁰ A distinct cleft or indentation marks the border of the HH attachment to the hypothalamus (Fig. 1A). Using this cleft as the starting point, we use the stereotactic trajectory view to determine the angle the disconnection will follow.

The resection begins by using a grasper through the working port of the endoscope. We start at the posterior edge of the HH and work anteriorly. This cycle is repeated until the pial surface on the deep side of the HH is reached. As the disconnection proceeds deeper, the remaining disconnected HH falls away medially from its hypothalamic attachment. We resist the temptation to pull out large chunks of the HH as it is disconnected. Doing so makes the interface swing laterally and increases the difficulty in disconnecting the most inferolateral attachment. Once the HH is disconnected, it is grasped and the endoscope/grasper complex is removed from the ventricle in one piece. If the HH is too large to fit through the foramen, it is morcellized before it is removed. Irrigation

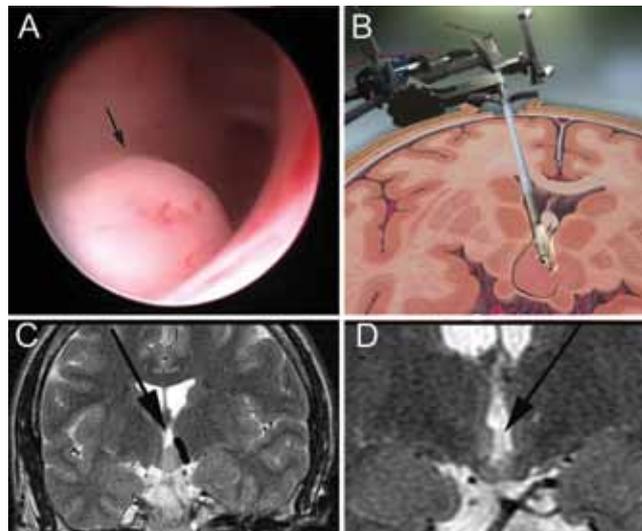


FIG. 1. **A:** Endoscopic view of a Type II HH through the right Monro foramen. The attachment to the left hypothalamus is easily distinguished (*arrow*). **B:** Illustration depicting the surgical arrangement of the stereotactic-tracked endoscope, robotic endoscope arm, and angle of dissection down the wall of the hypothalamus. (Reprinted from "Hypothalamic hamartoma." *Barrow Magazine* 17:12–13, 2005. Used with permission from Barrow Neurological Institute.) **C:** Preoperative coronal T2-weighted MR image showing a 1-cm Type II HH with the angle of dissection (*arrow*) and intended cleavage plain (*black line*). **D:** Postoperative MR image confirming complete resection of the HH (*arrow*).

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with or without coagulation is used to stop any bleeding. A ventriculostomy catheter is typically left in place and removed the next day.

One surgical pearl needs to be emphasized: the HH cannot reliably be distinguished from the hypothalamus based on the difference in the color or consistency. Hence, such cues cannot be relied on to guide resection. It is best to think of the resection as a straight-line disconnection guided by the initial angle determined by stereotaxy and proceed down that line until the deep pia/arachnoid surface is reached. By not breaching the pia/arachnoid surface, deeper structures such as the optic tract and perforating vessels remain beyond the reach of the instruments. Breaching this surface and damaging the perforating arteries can result in small infarctions of the basal ganglia and internal capsule. Such infarctions are often, but not always, clinically silent.²¹

If any part of the HH is positioned superior to the mammillary body, the disconnection must be shallow over the mammillary body to avoid its injury. However, many of these patients are so clinically and socially impaired that clinically significant damage to a mammillary body or fornix would not be evident. For this reason, it is reasonable to be more aggressive in pursuing resection or disconnection and in tolerating damage to relieve epilepsy in severely affected patients.

Transcallosal Resection

The transcallosal, interseptal, interforaminal approach is the preferred approach for large HHs with a significant intraventricular component located superior to the level of the optic tracts. This approach can be used alone to treat large Type II lesions. Many Type III and IV lesions require a staged approach. If the lesion is entirely medial to the line of sight down the wall of each hypothalamus, then a large Type III or IV lesion can be disconnected during 1 operation. In young patients (< 6 years old) and in patients with a small residual cavum septum, the leaves of the septum pellucidum are easily separated (Fig. 2). This feature facilitates safe separation of the fornices. As the patient ages, the interforaminal dissection becomes more difficult.

In most cases, the HH is primarily attached to 1 side of the hypothalamus. This side is placed up. If an equal bilateral attachment is present, we place the dominant hemisphere up. We use a large shoulder bolster to position all patients undergoing interhemispheric approaches

in the semilateral decubitus position. The head is turned so that the falx is parallel to the floor, and the head is tilted up approximately 45° (Fig. 3A). This position requires considerable rotation, flexion, and side bending of the neck. We monitor somatosensory evoked potentials during positioning of all patients to ensure that aggressive positioning does not compromise the patient.

The incision is planned using stereotactic guidance to avoid large frontal bridging veins. In general, we plan a coronal incision placed just behind the hairline that allows two-thirds of the sagittal dimension of the craniotomy to be anterior to the coronal suture and two-thirds of the coronal dimension of the craniotomy on the dependent side of the head. We place bur holes directly on the sinus at either end of the exposure and turn a craniotomy with the footplate cutting away from the sinus. The dura is opened in a U-shaped flap based on the sinus and tacked back. Care is exerted to avoid taking large bridging veins or cutting into large venous lakes.

Microsurgical dissection of the dependent hemisphere from the falx is straightforward. The cingulate gyri can be densely adherent, and dissection may be difficult. If clean dissection is impossible we prefer to go through the nondominant cingulate rather than damage both cingulate gyri. Both pericallosal arteries are identified and separated widely. We place cotton balls at the deep anterior and posterior limits of our dissection to keep the hemispheres separated.

Using stereotactic guidance with the microscope at the highest magnification and gross anatomical clues, we perform the callosotomy with the aid of a small dissector. It is key to be exactly in the midline as one proceeds (Fig. 3C). If the midline dissection is performed at high magnification, a blue-gray line representing the interforaminal space can be appreciated. It is easier to enter this space anteriorly. After entry, gentle dissection is continued posteriorly and inferiorly until the roof of the third ventricle is encountered. As the roof of the third ventricle is approached, the fornices will be on either side of the dissection.

Continuing the dissection into the third ventricle and separating the internal cerebral veins posteriorly gently separates the fornices. It is important to maximize the transforaminal working space so that the fornices will not be damaged during HH removal. The choroid plexus of the third ventricle posteriorly and the anterior commissure should be clearly visualized (Fig. 3D). We place a re-



Fig. 2. Coronal T2-weighted MR images obtained in patients with an HH requiring transcallosal resection. In 2 patients (**A** and **B**), signal from the CSF (arrows) is visible between the leaves of the septum. There is no discernible signal from CSF in the third patient (**C**). Interseptal interforaminal dissection is thought easier in patients with a discernible signal from CSF in the septum.

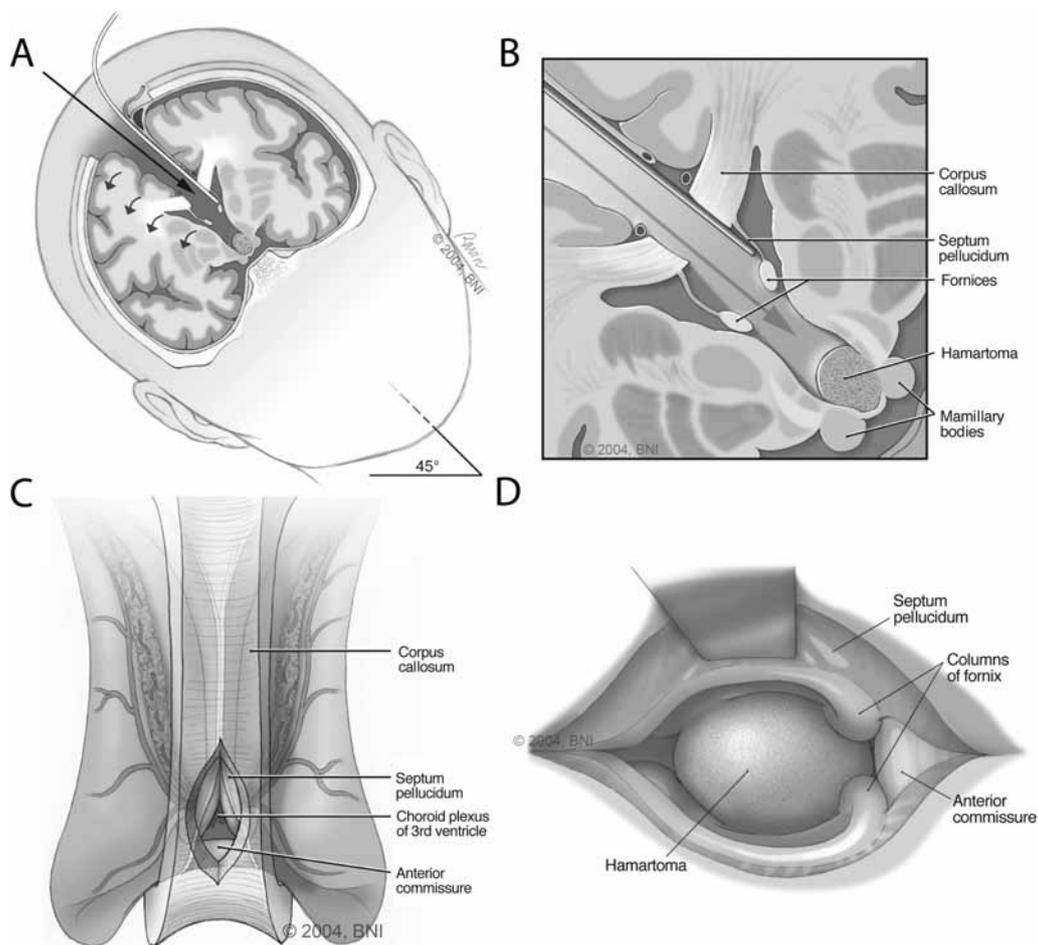


FIG. 3. **A:** Illustration of the appropriate head positioning (*upper left*) and use of gravity to retract the “downside” hemisphere during the transcallosal approach. **B:** Close up showing the excellent line of sight afforded large Type II lesions and the proximity of the fornices to the inferior septum. **C:** The callosotomy must be precisely midline and start anteriorly to arrive at the interseptal space. **D:** Once the fornices have been separated, the anterior commissure and the entire HH-hypothalamus interface should be visible. Reprinted from Ng T et al: *BNI Quarterly* 20:13–17, 2004. Used with permission from Barrow Neurological Institute.

tractor against the falx extending inferiorly onto the “upside” leaf of the septum (Fig. 3C). A cottonoid is trapped under and extended beyond the retractor tip to gently elevate and protect the “upside” fornix.

Tumor resection proceeds by centrally debulking with an ultrasonic aspirator. Next, the upside HH-hypothalamus interface is dissected using a combination of ultrasonic aspiration, dissection, and suction. Stereotactic guidance is used to plan the angle of dissection. Great care is taken to identify the piaarachnoid membrane on the deep and lateral surface of the HH. This should be inferior to the level of the optic tract. Once a piaarachnoid plane is identified, it can be followed 360° to disconnect the HH completely. Posteriorly, the mammillary bodies can be differentiated from the HH by their lighter color. The perforating arteries of the basilar and posterior cerebral arteries are adjacent to the deep and lateral surfaces of the HH. They can be avoided by careful subpial dissection and leaving the pia intact. The same is true anteriorly for the infundibulum and laterally for either optic tract.

It is a long reach to the inferior margin of large Type III and IV HHs and often requires working at the tips of

the microsurgical instruments with a reduced amount of control. If we are unsure of the safety of further removal, we stop the removal and will often leave the HH in situ. If the inferior portion can be easily dissected from the piaarachnoid on its deep surface, we remove it (Fig. 4). We typically leave a closed ventriculostomy in the resection cavity and remove it the next day.

Skull Base Approaches for Resection

Several skull base approaches to Type I, III, and IV HHs are used. We have performed variations of the orbitozygomatic, pterional, supraorbital eyebrow, and recently subtemporal approaches. Each approach has distinct advantages and disadvantages. Currently, we favor the modified orbitozygomatic craniotomy to maximize working space and light, minimize brain retraction, and to achieve as low and lateral of an angle as possible to lesions with bilateral attachment. For lesions with ipsilateral attachment, the supraorbital eyebrow approach is sufficient. Recently we had 1 patient with a temporal arachnoid cyst, which offered a perfect working corridor to approach an HH with bilateral attachment.

Surgical approaches to HHs

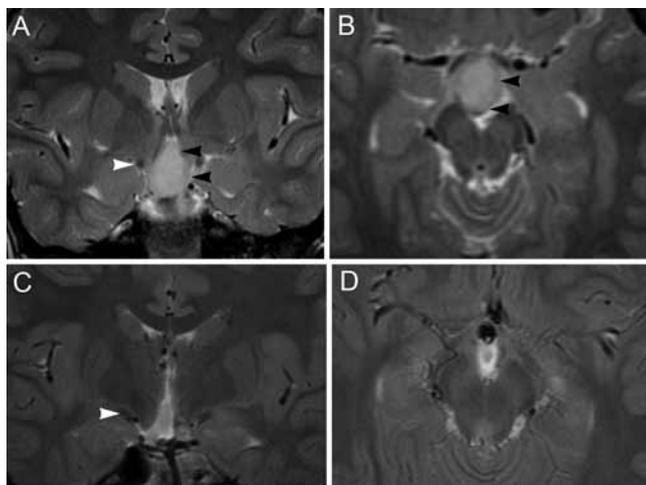


Fig. 4. Preoperative (**A and B**) and postoperative (**C and D**) T2-weighted MR images of a large Type II HH completely resected via the transcallosal approach. The HH is hyperintense (*black arrowheads*) compared with the normal surrounding structures including the optic tract (*white arrowheads*).

The patient is positioned with the ipsilateral shoulder elevated with a sandbag, the head rotated, and the neck extended so that the ipsilateral malar eminence is placed directly up. In the case of eyebrow incisions and supraorbital craniotomies, the nose is placed directly up and the incision is placed in the superior margin of the eyebrow. For others, a standard behind-the-hairline incision is performed.

The key to successful visualization of the inferior hypothalamus, mammillary body, optic tract, and pituitary stalk is achieving a very flat or even upward-looking trajectory. This trajectory is best obtained through a supraorbital craniotomy by extradural drilling of the ridges formed by the orbital part of the anterior skull base. In the case of the orbitozygomatic approach, it is performed by removing the orbital rim and orbital roof.¹¹ The modified orbitozygomatic approach and a complete sylvian fissure dissection allow the most lateral and upward angle for disconnection of lesions with bilateral attachments (Fig. 5).

Standard subfrontal dissection and wide splitting of the proximal sylvian fissure are performed. In a stepwise fashion, the internal carotid artery is dissected along its course until at least 1 cm of both the ACA and middle cerebral artery are free. Likewise, the ipsilateral optic nerve is followed posteriorly dissecting the chiasm and ipsilateral optic tract as it passes just lateral to the hypothalamus. To follow the optic tract back requires working in the opticocarotid window and in the window above the internal carotid artery bifurcation above and posterior to the ACA. The tumor emanating from the hypothalamus should be evident at this point.

Great care is taken to dissect posteriorly any perforators from the middle cerebral artery, posterior cerebral artery, and posterior communicating arteries from the tumor capsule. The capsule is coagulated and incised. Intratumoral debulking is performed using ultrasonic aspiration, suction, and dissectors. Once debulked, the superior margin of the tumor is defined by incising the capsule immediately inferior to the optic tract.

Working along the superior margin is challenging and is blind medial to the lateral edge of the optic tract. We have found down-pushing microsurgical curettes to be helpful in transecting the hamartoma from the hypothalamus while watching the tract to ensure that it is not tractioned downward.

The posterior resection margin should be the mammillary body if it is not involved in the hamartoma. It is difficult to see and may only be evident as the intratumoral resection proceeds and space is developed enough to “feel” the ipsilateral mammillary body with a dissector or to see it via the endoscope. If it is involved (evident from the MR images), the disconnection will proceed until it is encountered. The mammillary body is a slightly lighter color than the hamartoma and usually can be distinguished with maximal magnification of the microscope. It is easier to see and to avoid the ipsilateral mammillary body than the contralateral mammillary body.

Anteriorly, the stalk should be visualized and avoided. The resection should continue medially until the third ventricle is entered. If the hamartoma is bilateral, dissection continues until the contralateral pia is reached. A pial plane separates the HH from the contralateral optic tract. As long as this plane is respected, the optic tract will not be injured. At this point, the tumor is usually disconnected from the hypothalamus.

The remaining inferior “lump” can be resected in a subpial fashion to protect the contents of the prepontine cistern beyond the piaarachnoid layer. The same tenets discussed under *Transcallosal Resection* apply to the remaining disconnected portion of the HH.

Again, it is important to remember that a HH cannot be distinguished from normal hypothalamus under microsurgical view. Only the abnormal anatomy that it forms allows the surgeon to determine where to stop resection. Careful evaluation of the patient’s preoperative MR imaging study and use of intraoperative stereotactic guidance help clarify the aforementioned limits of resection.

Results

Surgical Procedures

Of the 165 patients with symptomatic HHs, 14 underwent skull base approaches as their initial surgery. Of those 14 patients, 3 required a second approach (endoscopic disconnection of residual HH). Fourteen patients underwent GKS as their initial treatment.² Three of these patients had subsequent endoscopic approaches. Ninety patients underwent endoscopic approaches as their initial surgery. Seven patients had additional procedures (GKS for residual HHs in 5, orbitozygomatic craniotomy in 1, and transcallosal approach in 1).

Forty-seven patients initially underwent a transcallosal approach. Eleven patients required subsequent procedures (GKS for residual tumor in 1, orbitozygomatic craniotomy in 3, a second contralateral transcallosal approach in 2, and endoscopic approach in 4). Of the 165 patients, 26 (15.8%) required more than 1 procedure. Twenty-two patients required 2 procedures, 3 patients required 3 procedures, and 1 patient required 4 procedures.

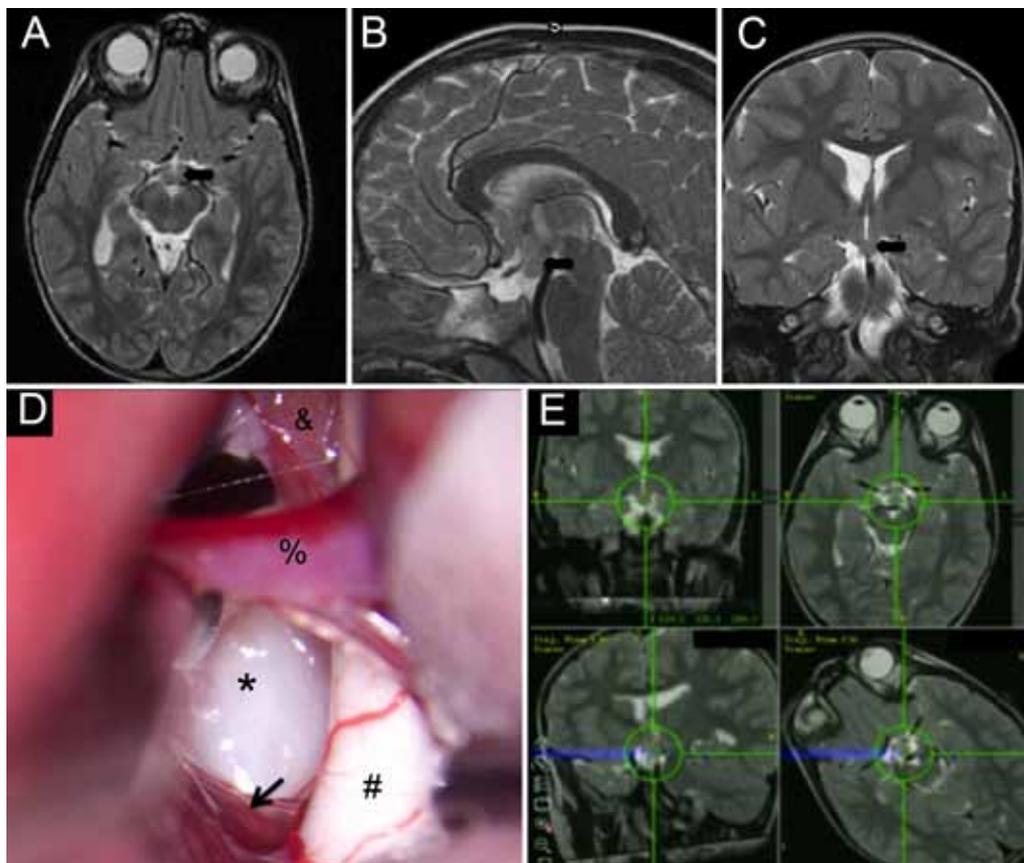


FIG. 5. **A–C:** Preoperative T2-weighted MR images of a small Type I HH (arrows) with bilateral attachment. This required a low, lateral trajectory to safely address each connection and was completely resected from a right modified orbitozygomatic approach. **D:** High-magnification view of the operative site demonstrating the tight working space but excellent view of the hamartoma (asterisk), infundibulum (ampersand), ACA (percentage sign), optic tract (number sign), and perforating vessels (arrow) swept posteriorly. Most of the operation takes place superior and posterior to the ACA. However, the anterior portion of the HH is addressed by moving the ACA posteriorly and working anterior to it. **E:** Stereotactic illustration (lower right) of the angle of attack. The blue lines represent the working trajectory.

Outcomes

Updated epilepsy outcome data for our entire series will be reported in a future publication. Previously, however, we published data on the first 26 patients undergoing a transcallosal approach.²⁰ The mean postoperative follow-up interval was 20.3 months (range 13–28 months). Fourteen patients (54%) were completely seizure free, and 9 (35%) had at least a 90% improvement in total seizure frequency. Parents reported postoperative improvement in the behavior of 23 patients (88%) and in the cognition of 17 patients (65%). Transient postoperative memory disturbances occurred in 15 patients (58%), but persisted in only 2 (8%). Two patients (8%) had persistent endocrine disturbances that required hormone replacement therapy (diabetes insipidus and hypothyroidism in 1 each).

In the first 37 patients who underwent endoscopic resection,²¹ 18 (48.6%) were seizure free at last follow-up (median 21 months, range 13–28 months). Seizures were reduced in 34 patients (91.9%). The mean postoperative stay was shorter in the patients undergoing endoscopy than in the patients undergoing transcallosal resection (mean 4.1 days vs 7.7 days, respectively; $p = 0.0006$). The main complications were permanent short-term memory

loss in 3 patients and small thalamic infarcts in 11 patients (9 were asymptomatic).

Of the 10 patients who underwent an orbitozygomatic craniotomy for HH,¹ 4 (40%) are seizure free and 4 (40%) have had more than a 50% reduction in seizures. One patient had no significant change in seizure frequency, and another patient died unexpectedly 2.8 years after surgery. Residual complications included diabetes insipidus, poikilothermia, visual field deficit, and hemiparesis in 1 patient each. Eight families (80%) reported improved quality of life.

Discussion

Initially, attempts at surgical cure of epilepsy for patients with HH were largely unsuccessful and had a high complication rate.^{12,22} Individualizing the approach based on the anatomy of the HH and frequently using several approaches in a single patient allowed seizure-free rates of more than 50% in patients treated in the first half of our series. By following the surgical procedures we have outlined above, we aim to improve the outcomes for patients undergoing surgery for these difficult lesions (Table 1).

Surgical approaches to HHs

TABLE 1: Simplified treatment paradigm at Barrow Neurological Institute indicating the first approach recommended for HHs based on their type and size*

HH Type	Approach to Small Lesions	Approach to Large Lesions
Type I	orbitozygomatic GKS	orbitozygomatic
Type II	endoscopic GKS	transcallosal
Type III	endoscopic ± orbitozygomatic GKS	transcallosal ± orbitozygomatic
Type IV	not applicable (Type IV = giant)	staged approach: address primary component first

* Gamma Knife surgery may also be used for more complex or giant lesions as salvage therapy after debulking/disconnection, and GKS may be considered for small Type I lesions, although to date no Type I lesion has been found suitable at the center. Reprinted with permission from Abula et al: *J Neurosurg (Suppl)* 113:207–214, 2010.

The difficulties encountered in early reports of small series of patients are likely the natural and inevitable results of the “learning curve.” One purpose of this manuscript is to share the technical nuances that we have learned, sometimes painfully, during the accrual of a large patient population.

We counsel patients and families that their initial treatment may be the first of multiple treatments to achieve the safest, most efficacious outcome. We favor superior approaches to HHs with a significant hypothalamic attachment. Endoscopy is the preferred method but its use is limited by the size of the third ventricle. Larger lesions are more difficult to disconnect completely using the endoscope. However, patients undergoing endoscopic approaches have shorter hospital stays, and fewer complications than open transcallosal approaches.²¹

Factors favoring a transcallosal interforaminal approach include young age (children tolerate transcallosal resection better than adolescents and adults), a bilateral HH attachment, and large lesions that fill or nearly fill the third ventricle. The presence of a residual cavum septum, helping to minimize manipulation and traction on the fornix, is also favorable for transcallosal resection.

Factors favoring transventricular endoscopic resection include small HH lesions, unilateral attachment, and generously sized ventricles. Type II lesions with a unilateral attachment are ideal for an endoscopic approach from the contralateral ventricle.

At our institution, GKS is used to treat small lesions distant from radiosensitive structures in patients with higher cognitive function. The patient must have a stable clinical picture that will allow time for the effects of radiosurgery to occur without further deterioration. Patients must not be severely affected by epilepsy at the time of treatment.

Often, patients harboring HHs are so devastated by severe epilepsy and frequent rage attacks that they are essentially noncommunicative and, other than interactions with their caregivers, socially isolated. In such cases, dam-

age to a fornix is seldom a clinically significant side effect or even detectable. In this situation, cure of epilepsy is the goal regardless of any potential damage to the fornix or of endocrinological problem from manipulation of the hypothalamus.

Conclusions

The use of 1 or more surgical approaches in appropriately selected patients with symptomatic HHs can provide excellent results. Cure or control of seizures and improvement in quality of life are seen in a large majority of patients. Complications occur at an acceptable rate and can be minimized by a thorough understanding of the complex regional anatomy and anatomical considerations specific to each approach.

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: Wait, ReKate. Acquisition of data: Wait, Abula, Nakaji, ReKate. Analysis and interpretation of data: Wait, Abula, ReKate. Drafting the article: Wait, Killory. Critically revising the article: Abula, Nakaji, ReKate. Reviewed final version of the manuscript and approved it for submission: ReKate.

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