Hypothalamic hamartomas. Part 2. Surgical considerations and outcome

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Hypothalamic hamartomas are uncommon developmental heterotopic masses composed of an intermixed array of neurons, glia, and myelinated fibers closely associated with the mammillary bodies. Gelastic seizures, the hallmark feature of hypothalamic hamartomas, commonly present in early childhood. However, patients usually also display a disabling clinical syndrome, which may include various other types of refractory seizures with secondary generalization together with progressive cognitive, behavioral, and psychiatric dysfunction. The hamartoma itself has been unequivocally shown to be intrinsically epileptogenic. Over the past 2 decades there has been considerable effort to develop neurosurgical techniques to treat the epileptic syndrome effectively as well as to improve the neurocognitive and behavioral outcome.

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IN this review we discuss the various microsurgical approaches used to remove the hamartoma. In addition, we review the experience with less invasive surgical strategies, such as neuroendoscopic disconnection and SRS. These techniques have also been shown to yield good outcome in seizure control and improvements in behavior, cognition, and overall development. Younger children may particularly benefit from aggressive neurosurgical management in an effort to reduce or prevent the sequelae commonly associated with HHs.

Patients with HH suffer from devastating medically intractable epilepsy as well as substantial and progressive behavioral, cognitive, and psychiatric dysfunction. Hence, a lot of effort has been given in developing new and refining existing surgical techniques for the treatment of these problematic diencephalic lesions. In 1967, North-

field and Russell⁴⁸ performed the first successful removal of an HH causing CPP. In 1969, Paillass et al.⁴⁹ described the clinical, radiographic, and histological findings in a patient who underwent microsurgical excision of an HH. Over the next 2 decades, a handful of other investigators reported their efforts to control the gelastic seizures by excision of the HH.^{46,57,58,69} Interest in the surgical treatment of HHs expanded noticeably in the 1990s as a result of the widespread availability of high-resolution MRI, enabling accurate identification of HHs.

In this review we will discuss the different microsurgical strategies used in the treatment of HHs and associated refractory gelastic seizures. In addition, we will review alternatives to open surgery such as endoscopic disconnection of the HH and other less invasive techniques, including stereotactic radiosurgery and radiofrequency thermocoagulation. Recent advances and efforts have resulted in minimizing surgical morbidity with improved outcomes. The clinical, electrophysiological, and neuroimaging characteristics of HHs have been outlined in Part I of this 2-part review.⁴¹

Abbreviations used in this paper: CPP = central precocious puberty; DBS = deep brain stimulation; DI = diabetes insipidus; GKS = Gamma Knife surgery; HH = hypothalamic hamartoma; LINAC = linear accelerator; SRS = stereotactic radiosurgery; VNS = vagal nerve stimulator.

Microsurgical Resection of HH

Surgical intervention appears to provide the best opportunity for achieving seizure freedom and halting (and perhaps reversing) the progressive decline in neurocognitive function as well as improving the coexisting behavioral and psychiatric syndrome. Broadly speaking, microsurgical approaches can be divided into those that reach the diencephalic mass from below and those that reach it from above.⁶⁵ Others advocate that disconnection from the mammillary bodies rather than complete excision of the HH is sufficient to eliminate seizures, and that this procedure carries less surgical morbidity. Still others believe that a strictly noninvasive modality such as SRS is the optimal choice for managing these difficult lesions. Ultimately, the choice of surgical approach should be tailored to each patient depending on the size of the hamartoma, its anatomical relationship to the hypothalamus and surrounding neurovascular structures, the age of the patient, and the surgeon's experience and comfort with the operative technique.⁷⁶

Pterional Approach

Given the familiarity of conventional frontotemporal and pterional approaches, it is not surprising that these techniques were commonly used in the initial clinical series reporting microsurgical resection of HHs (Fig. 1).^{36,47} Some authors reported that addition of a subfrontal, subtemporal, transsylvian, or other skull base access could facilitate excision of the hypothalamic lesion.^{23,39,40} Although it does provide the shortest and most direct route to the suprasellar cistern, the pterional approach does

Fig. 1. Patient treated via the pterional approach. This 3-year-old boy presented with gelastic seizures at the age of 1 year. He developed myoclonic spasms at 19 months, with regression of fine motor tasks accompanied by psychomotor and speech retardation. Sagittal and coronal MRIs show a Delalande and Fohlen Type I pedunculated HH (**upper panel**). Postoperative MRIs obtained following a pterional craniotomy for resection of the hamartoma (**lower panel**). The patient was seizure free after surgery and had marked improvement in behavior.

have inherent limitations. The narrow surgical corridor between the internal carotid artery, optic nerve and chiasm, third cranial nerve, and infundibulum limits access to the third ventricle and the intraventricular component of the HH. Identifying the margins of the hamartoma is often challenging, particularly if it is broadly attached to the hypothalamus and mammillary bodies. Using the pterional approach to resect the HH, Palmmini et al. reported that 3 of their 13 patients achieved seizure freedom, and a > 90% reduction in seizure frequency was noted in the remaining 10 children.⁵¹ All patients demonstrated significantly improved behavior and cognition following microsurgical excision of the HH. However, significant morbidity occurred in 7 patients in whom the transsylvian approach was used, including transient third nerve palsy, thalamocapsular infarcts, postoperative central DI, and hyperphagia (Fig. 2).⁵¹

The Barrow group followed 10 patients who underwent either an orbitozygomatic approach alone or combined with a transventricular endoscopic excision of the HH.¹ After a mean follow-up of 37 months, 4 patients became seizure free. All 4 had total or near-total resection of their lesions with complete disconnection of the hamartoma. Cognitive outcome was either improved or unchanged in 8 patients, and 2 had improvements in behavior. Nine of the 10 patients' families reported some improvement in quality of life. Complications included increased appetite, DI, visual field deficit, and capsular infarct. One patient required ligation of the supraclinoid portion of the internal carotid artery, but fortunately had good collateral flow and no ensuing deficits. Based on their case series, these authors concluded that HHs attached below the third ventricle (Delalande and Fohlen Type I) would benefit from the orbitozygomatic approach, but that most other patients with HH would benefit from either a superior approach or from endoscopic or stereotactic radiosurgical procedures.

Overall, despite excellent outcomes in terms of seizure control, the frontotemporal approach resulted in major complications. These suboptimal results created a need to develop alternate surgical strategies to improve seizure freedom rates while limiting surgery-related morbidity.^{35,42} Nevertheless, a pterional approach seems best for targeting pedunculated HHs that cause CPP. Even a

Fig. 2. Complications of pterional approach. This 7-year-old boy, in whom gelastic seizures had been diagnosed at the age of 5 months, developed worsening speech and language difficulties along with aggressive behavior. Preoperative MRI showed a Delalande and Fohlen Type II intrahypothalamic HH (**left**). The patient was seizure free and had significantly improved behavior after microsurgical resection of the hamartoma was performed using a pterional approach. However, he developed persistent right hemiparesis as a result of a left thalamocapsular infarct (**arrow, right**).

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partial resection has been shown to relieve the endocrinological disturbance.²⁵ Pedunculated HHs seem more amenable to complete resection than sessile ones.

Transcallosal Approach

In 2001, Rosenfeld et al.⁶⁸ first reported their experience using an anterior transcallosal, transseptal, interforaminal approach to remove HHs through the third ventricle. Their approach consisted of a small (15–20 mm in length) postgenual callosotomy followed by midline transseptal dissection and separation of the fornices, which allowed entry through the roof of the third ventricle with subsequent removal and/or disconnection of the HH (Fig. 3).⁶⁷ This elegant technique offers not only an exceptional intraventricular view of the hamartoma from above, but compared with the approaches from below, allows adequate debulking or disconnection of the HH while reducing risk of injury to the mammillary bodies, pituitary stalk, and optic chiasm (Fig. 4). Moreover, the incidence of cerebral infarction and oculomotor nerve palsy is greatly reduced by avoiding manipulation of the neurovascular structures in the suprasellar cistern and interpeduncular fossa. However, there is an inherent risk of septal, forniceal, or mammillary body injury resulting in short-term memory problems. The risk of postsurgi-

cal memory deficits can be reduced by using a modified subchoroidal approach instead of splitting the fornices.⁹

In 2003, the Melbourne group reported their results after using the anterior transcallosal, transseptal, interforaminal approach in 29 patients followed for a mean of 30 months.²⁷ They achieved a complete or near-complete (> 95%) resection in 18 patients (62%). Of the 29 patients, 15 (52%) were seizure free and another 7 (24%) had a > 90% decrease in frequency of seizures following surgery. Complications included thalamic infarction, increased appetite, and short-term memory deficits.⁶⁶ Cognitive outcomes studied in 6 older patients (mean age 24 years) in a follow-up study showed mild improvement in perceptual and visuospatial function, but there was no evidence of improvement in multidomain cognition, which had been seen in younger patients.⁴ Three of the patients had memory deterioration postoperatively, most likely due to damage to the fornices or the mammillary bodies during surgery. The authors concluded that SRS may be the preferable approach for older adolescents and adults.⁴

After their initial study in 10 patients,¹⁸ in 2006 the team at the Barrow Neurological Institute published surgical outcomes in 26 patients and demonstrated a direct relationship between the extent of HH excision and seizure outcome.⁴⁴ Fourteen (54%) of the 26 patients were seizure

Fig. 3. Illustration of transcallosal transseptal interforaminal approach used for resection of HHs, with relevant neuroanatomical structures. Adapted from Wait et al: *Neurosurg Focus* 30(2):E2, 2011. Modified with permission from Barrow Neurological Institute.

FIG. 4. Patient treated via the transcallosal approach. Axial T2-weighted MRI showing a small Delalande and Fohlen Type II HH (A). Intraoperative photographs obtained following a transcallosal interforaminal approach before (B) and after (C) microsurgical resection of the mass.

free and another 9 (35%) had > 90% reduction in seizure frequency. Improved behavior and cognition was noted in 23 (88%) and 17 (65%) patients, respectively. Fifteen (58%) experienced memory disturbance after surgery, but this only persisted in 2 (8%). One patient had persisting hypothyroidism and another had central DI requiring hormone replacement therapy. The investigators demonstrated a correlation between completeness of excision of the HH and seizure freedom. They also noted a strong inverse correlation between the duration of epilepsy and volume of HH and the probability of a seizure-free outcome. Whereas complete resection of larger hamartomas can be accomplished safely in younger patients by using the transcallo-

sal interforaminal approach, the authors noted that in older patients there is an increased risk of memory impairment from fornix injury because the leaves of the septum pellucidum are not as easily separated.⁴⁴

Yao and colleagues⁸⁰ reviewed their series of 37 patients with HH who underwent an interhemispheric approach. They concluded that the transcallosal interforaminal approach is effective in controlling gelastic seizures and has few complications. The most common adverse effect of surgery was electrolyte imbalance. In the past few years, several other groups have reported good outcomes with the anterior transcallosal, transseptal, interforaminal approach.

Transtemporal, Transchoroidal, Transamygdala Approach

Hamlat and colleagues²⁶ recently described their experience with a transamygdala extension of a transtemporal, transchoroidal approach for radical resection of 5 suprasellar, retrochiasmatic, diencephalomesencephalic lesions, including 1 HH. This approach may be valuable for large HHs occupying the interpeduncular cistern.

Endoscopic Transventricular Approach

In 2002, Akai et al.³ first reported using an endoscope for transventricular biopsy of an HH in a 5-year-old girl with gelastic seizures. The hamartoma was then treated with stereotactic radiosurgery by using a LINAC. Unfortunately, the patient's seizure and behavioral problems remained unchanged for 6 months. She eventually underwent a partial resection with laser coagulation of the HH in which a neuroendoscopic approach was used. Postoperatively, a significant reduction in the frequency of her seizures was noted together with marked improvement of her violent behavior.

In 2006, the Barrow group published their results using endoscopy for HHs.⁶³ In their series, 44 patients underwent an endoscopic transventricular approach in which frameless stereotaxy was used for resection of the HH that was causing refractory gelastic seizures. Of the 14 patients (31.8%) who had complete resection, 13 became seizure free following surgery. The remaining 30 patients underwent an endoscopic disconnection rather than resection of the HH (see below).

Cappabianca and colleagues¹⁰ provided an excellent review of the use of neuroendoscopy to treat intraventricular lesions. They noted that not all patients with HHs are ideal candidates for endoscopic resection. These authors emphasized that this approach should be considered for small HHs with a unilateral attachment to the hypothalamic wall. Furthermore, they cautioned that it is imperative that a space between the bottom of the hamartoma and the pial surface of the interpeduncular cistern must exist for an endoscopic approach to remove HHs to be considered. Likewise, they reported that a working distance of at least 6 mm should be present between the top of the HH and the roof of the third ventricle.

Clearly, no single microsurgical approach can provide access to the entire variety of HHs. Surgical approaches must be carefully chosen based on the site, type of HH (sessile or pedunculated), and its extensions. Over

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the years, however, the transcallosal, interforaminal approach has become the preferred route for resection and/or disconnection of HHs in many epilepsy surgery centers, including ours.

Open and Endoscopic Disconnection of HH

Delalande and Fohlen¹⁵ hypothesized that disconnection (without excision) of the HH could be sufficient to isolate the intrinsically epileptogenic lesion and thereby result in good seizure outcomes. In 2003 they published their series of patients who underwent disconnection of the intraventricular component of the hamartoma.¹⁹ Of 18 patients, 14 underwent open surgical disconnection, 3 had a pure endoscopic disconnection procedure, and 1 had complete excision of the hamartoma. Altogether, nearly half of the patients (8 of 17) were seizure free after open and/or endoscopic disconnection of the hypothalamic mass. Moreover, the vast majority of patients attained marked improvement in social and behavioral outcomes. Surgical complications included ischemic stroke in 2 patients, meningitis in 1, and transient DI in 2 cases.¹⁹

In 2004, Choi et al.¹² published their initial results with endoscopic disconnection in 4 patients with HH-related refractory seizures. In their follow-up study,⁷³ the Korean group reported on 14 patients harboring a sessile HH, 11 of which were treated with endoscopic disconnection (primary treatment in 9 patients, and 2 others underwent surgery following initial GKS). Six patients became immediately seizure free and 4 others had a good outcome (Engel Class II). Two patients underwent endoscopic disconnection following radiosurgery; their gelastic seizures disappeared after the disconnection. All 11 patients had placement of a single depth electrode in the HH prior to and after the endoscopic disconnection. These authors confirmed (via the results obtained from the depth electrodes) the intrinsic epileptogenesis of HHs, which was contained by hindering the propagation of the epileptic activity via simple disconnection of the HH. Overall, these authors noted that patients with smaller hamartomas had better overall outcome and that an endoscopic approach offered a safe and effective alternative.

In a follow-up paper,⁴⁵ the Barrow group reported the long-term results in 37 patients who underwent endoscopic disconnection and resection for HH. Complete disconnection and resection was achieved in 12 patients. Twenty-six patients (70.3%) had > 90% reduction in seizure frequency (18 of 37 [48.6%] became seizure free), 8 patients (21.6%) had between 50% and 90% reduction in frequency, 2 remained unchanged, and 1 worsened clinically. The most significant postoperative morbidity was persistent short-term memory loss in 3 patients. Two additional patients had transient memory impairment. Of the 12 patients who underwent both disconnection and complete resection, 8 (67%) became seizure free.

Similar results were obtained by Shim and colleagues,⁷³ who performed endoscopic disconnection in 11 patients by using neuronavigation guidance. Stabell et al.⁷⁴ noted a significant decline in cognitive function (decrease in verbal IQ, immediate and delayed recall, and color naming) in a young girl with HH who underwent

incomplete endoscopic disconnection of the hamartoma. She also had persistent hemiparesis and oculomotor paresis after surgery.

Again, not all lesions are amenable to endoscopic disconnection. The feasibility of successful disconnection depends on a number of factors, including the plane and extent of attachment of the HH to the hypothalamus.¹⁴ Some large lesions may require a multistep approach in which several disconnection procedures are used, or a combination of microsurgical resection and endoscopic disconnection. They noted that patients with large HHs (> 15 mm in diameter) had poorer seizure outcomes.

Open and endoscopic disconnection surgery is a generally safe and effective surgical option for small, sessile HHs. However, completeness of the disconnection and/or removal appears to correlate with improved rates of seizure freedom. Again, a tailored approach based on the radiographic characteristics of the HH is recommended. However, as highlighted by Stabell and colleagues,⁷⁴ even this “less invasive” treatment modality may result in long-term neurological and cognitive deficits.

Stereotactic Radiosurgery

The elegance of selective targeting of the deep-seated mass in a minimally invasive manner together with the important risks associated with various surgical approaches prompted the use of SRS to treat gelastic seizures related to HHs. Both GKS and LINAC-based radiosurgery have been used by several groups. Additionally, brachytherapy by means of stereotactic implantation of radioactive sources within the hamartoma has been used by some investigators.

Gamma Knife Surgery

The group in Marseille pioneered the use of SRS in treating patients with intractable mesial temporal lobe epilepsy.⁶¹ The initial promising results obtained in these patients provided compelling support for the use of SRS in patients with HHs. Over the past 15 years, numerous centers have reported their experience with using GKS for its specific antiepileptic effect in patients with HH who were suffering from intractable epilepsy.

Successful treatment of HH-associated gelastic seizures by using GKS was first reported by Arita et al.⁶ in 1998. Their patient, a 25-year-old man with a small HH and long-standing history of medically refractory gelastic and tonic-clonic seizures, was treated with a dose of 18 Gy to the 50% isodose line. His seizures abated 3 months after the radiosurgical procedure and he remained seizure free at the 21-month follow-up with no new neurological or endocrine dysfunction. Twelve months after GKS, the hamartoma had completely disappeared.

In 2006, the group in Marseille published the long-term results of their prospective trial in which a total of 60 patients with HH and intractable epilepsy were enrolled.⁶² The median prescribed marginal dose was 17 Gy (range 13–26 Gy). The authors judiciously used a beam-blocking strategy to reduce the dose delivered to critical surrounding structures such as the mammillary bodies, tuber cinereum, fornices, and infundibulum as well as op-

tic nerves and chiasm. Thirty-one patients were evaluated for at least 3 years after radiosurgery; of these, satisfactory follow-up was available in 27. Only 10 (37%) of these 27 patients achieved seizure freedom; 6 others (22%) experienced a significant decrease in frequency of seizures. Although the majority had noteworthy improvement in behavior and cognition, the lesion appeared unchanged on follow-up MRI studies in most cases, except in 2 in which the hamartoma was slightly smaller. None of the patients had permanent complications from GKS; however, 4 (15%) experienced transient worsening of seizures. The authors advocated that GKS should be regarded as primary treatment for small and medium HHs, whereas larger lesions should undergo a staged approach with microsurgical disconnection (open or endoscopic) of the lower part of the hamartoma followed by radiosurgical treatment of the small upper part of the residual HH.⁶²

Several other groups have reported their experience with GKS for treating intractable epilepsy related to HHs.^{2,7,16,17,31,38,73,75} Taken together, these studies demonstrate that GKS is an effective treatment modality for selected patients with HH-associated epilepsy. However, it is important to remember that, similar to the complications of microsurgical resection of the HH, radiosurgery can result in permanent neurological sequelae.^{60,64} Also, there seems to be a dose-dependent response in which improved seizure control rates are attained with marginal doses > 16 Gy.⁵⁹ However, one of the main disadvantages is that clinical response can be very slow; the patient remains exposed to the risks of persistent seizures for up to 2 years after the radiosurgical procedure. In this regard, microsurgical resection has a clear advantage because of its ability to yield immediate postsurgical results.

Linear Accelerator–Based Radiosurgery

There have been fewer reports describing the use of LINAC-based SRS for treatment of HHs. As mentioned previously, in 2002 Akai et al.³ used radiosurgery to treat a 5-year-old girl with HH-related gelastic seizures after neuroendoscopic biopsy of the hypothalamic mass. At 6 months her symptoms were unchanged, and the authors proceeded with endoscopic resection and laser thermocoagulation of the lesion, with good results. In 2005, Selch et al.⁷² used LINAC-based SRS to treat gelastic seizures caused by sessile HHs in 3 patients. They prescribed 15–18 Gy at the 90%–95% isodose line. Two patients were seizure free at 15 and 17 months after radiosurgery, and 1 achieved an Engel Class II outcome at 9 months. None had any postradiosurgical complications. In 2008, Pappayannis et al.⁵² reported their experience with 4 patients with HH who were treated using a LINAC apparatus at doses between 12 and 18 Gy. None of the 4 patients had any meaningful clinical improvement.

Stereotactic Brachytherapy

A stereotactic brachytherapy approach in which ¹²⁵I seeds were used has been reported by Schulze-Bonhage and colleagues to achieve a highly focal, effective, and minimally invasive treatment option for patients with HHs.

In their most recent report, Schulze-Bonhage and co-

workers⁷¹ reported their cumulative experience with interstitial radiosurgery in 24 patients with a mean follow-up period of 12 months (range 3–60 months). All patients had intrahypothalamic hamartomas with a mean volume of 1.2 ml (range 0.4–3.8 ml). Seven patients had CPP and 2 had polydactyly suggesting Pallister-Hall syndrome. The procedure was repeated in 13 patients due to inefficacy of the initial treatment after 1 year. The treatment dose was 60 Gy to the surface of the hamartoma, with a mean placement time of 25 ± 6.7 days. After treatment, 12.5% of patients became completely seizure free and 25% had nondisabling partial complex seizures. Four patients (16.7%) had > 90% reduction in frequency and another 4 (16.7%) experienced > 75% reduction. Seven patients (29.2%) did not benefit from interstitial radiosurgery. Treatment effects occurred within 8 weeks.

Of the 13 patients who underwent reimplantation, only 1 continued to have seizures after the second implantation. All patients showed improvement in behavior and social skills. There was a reduction in the volume of HH in only 7 patients, which suggested that there was functional inactivation of the epileptogenic tissue without actual destruction. No perioperative morbidity was reported. Brain edema occurred in 5 patients, which subsequently resolved over the following few months. There was no evidence of hormonal disturbances; however, 4 patients experienced weight gain of 5–24 kg. There were no neurological or cognitive deficits following implantation. The authors remarked that the duration of epilepsy seemed longer in those patients with less improved outcome and cautioned that edema is more likely with larger lesions and with eccentric seed placement. These factors could increase the risk of neuropsychiatric deficits with implantation. They concluded that seizure control with interstitial radiosurgery may be inferior to microsurgery, but that there are fewer side effects associated with stereotactic brachytherapy. They observed that a better outcome was obtained in patients treated earlier in the course of their epilepsy.

A subset of patients with HH who present with a milder form of epilepsy and have less significant behavioral and/or cognitive comorbidities may perhaps benefit the most from a radiosurgical approach as their primary treatment modality.²⁰ Certainly, with more experience and further refinement of selection criteria, SRS will have a central role in treatment algorithms for the management of HHs.

Stereotactic Radiofrequency Ablation

Lesioning of the hamartoma by using stereotactic radiofrequency thermocoagulation rather than a direct microsurgical or radiosurgical approach has been used in some centers. This procedure has been used to treat patients with a variety of conditions such as intractable pain, movement disorders, refractory epilepsy, and metastatic brain tumors.^{5,32,54,56}

In 1999, Parrent⁵³ reported on a patient who continued to have disabling seizures despite partial excision of the HH, anterior temporal lobe resection, and orbitofrontal corticectomy. Later, stereotactic radiofrequency abla-

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tion of the HH was performed, resulting in progressive amelioration of the epileptic disorder during a 28-month follow-up.

In 2003, Kuzniecky and Guthrie³³ presented their experience with 12 children in whom progressive epileptic encephalopathy related to an HH was treated using thermocoagulation alone ($n = 4$) or supplemented with endoscopic partial resection ($n = 8$). Three patients were seizure free at a mean follow-up of 27.3 months (range 18–40 months). Three others had > 90% reduction in seizure frequency at a mean follow-up of 51.6 months (range 36–70 months). Two developed transient neurological deficits including oculomotor palsy and memory loss. One child died as a result of brainstem infarction. The authors concluded that in patients with small HHs, stereotactic thermocoagulation is a viable option.

The most extensive experience using MRI-guided stereotactic radiofrequency thermocoagulation for epileptogenic HH comes from Japan.^{21,22,24,28} In their most recent paper, Kameyama et al.²⁹ reviewed results from 25 consecutive patients with HH and gelastic seizures who were treated with radiofrequency thermocoagulation. They divided HHs into 3 types based on coronal MRI findings: intrahypothalamic, parahypothalamic, and mixed type. Complete seizure freedom was seen in 19 (76%) of 25 patients over a mean follow-up of 2.3 years. Transient postoperative complications included hyperthermia, hyperphagia, hyponatremia, Horner syndrome, and short-term memory problems. Six patients in whom CPP was diagnosed preoperatively showed no change in their endocrine status and continued requiring gonadotropin-releasing hormone agonist treatment. All 10 patients who had behavior disturbances preoperatively showed complete resolution of their behavioral abnormalities following radiofrequency ablation.

Wang et al.⁷⁷ recently reported on a 22-year-old man with a small sessile intraventricular HH presenting with intractable gelastic seizures. A depth electrode was inserted after local sedation and intrahamartoma epileptiform discharges were captured. Following radiofrequency thermocoagulation of the HH, he remained seizure free 12 months after surgery. Also, instead of ablating the HH, de Almeida and colleagues¹³ reported on an 18-year-old man who underwent a stereotactic disconnection of the HH, for which radiofrequency thermocoagulation was used. The procedure aimed at disconnecting the hamartoma from the hypothalamus, medial forebrain bundle, fasciculus princeps, and dorsal longitudinal fasciculus. These authors obtained a sustained improvement in seizure frequency and a reduction in aggressive behavior over a 2-year period.

Overall, radiofrequency ablation provides an effective, minimally invasive approach for the treatment of HHs. The results with stereotactic radiofrequency ablation, unlike with SRS, can be seen immediately following the procedure. However, drawbacks of the technique include inexact volume of tissue ablation and the need for multiple trajectories to treat larger hamartomas, thereby adding to the risk of injury to the surrounding neurovascular structures compared with a single pass.

Deep Brain Stimulation

The nondestructive and reversible nature of DBS has made it an attractive consideration for the surgical treatment of medically refractory epilepsy. Mechanistically, the rationale for the efficacy of DBS for epilepsy is similar to that seen with high-frequency stimulation for the treatment of movement disorders.^{34,70} The DBS treatment method is thought to impede seizure activity via long-term inactivation of neurons adjacent to electrodes following stimulation. This would presumptively result in an interruption of the pathological epileptogenic activity involving the classic circuit of Papez and associated neural sites. Thus far, only 3 groups have used this strategy to treat the devastating epileptic syndrome associated with HHs.

In 2004, Watts and coworkers^{78,79} reported, in abstract form, their experience in a patient who underwent direct implantation of a stimulating electrode into the HH. Early results showed improvement in seizure activity and social/communication skills 7 months after surgery. Unfortunately, no follow-up report has been presented on this patient. More recently, Khan and colleagues³⁰ described 2 patients with pharmacoresistant seizures due to HH who underwent DBS electrode placement adjacent to the ipsilateral mammillothalamic tract. Following high-frequency stimulation of the mammillothalamic tract, both patients experienced significant reduction in seizure frequency; one of them was seizure free for 10 months after surgery. Finally, Marras et al.³⁷ reported their experience with DBS in a 31-year-old woman with HH-related seizures. After 18 months, her complex partial seizures showed a decrease in frequency and intensity. However, there was no change in her overall seizure frequency (complex partial and gelastic seizures). No behavioral, endocrinological, or neurological side effects were noted. Certainly, further work needs to be done to determine the role of DBS in the treatment of epilepsy related to HHs.

Vagal Nerve Stimulation

Three groups reported their experience with a VNS for HH-related epilepsy. In 2000, Murphy et al.⁴³ first reported using a VNS on the left side as primary treatment in 6 children with HHs. Three had some improvement but the other 3 did not respond. However, the conduct in all 4 children with severe autistic behavior improved after VNS implantation. Brandberg et al.⁸ implanted a VNS in 5 children; none had any clinical benefit. Finally, Watts and colleagues⁷⁸ presented, in abstract form, two patients with HH who did not benefit from VNS therapy as either a primary or secondary procedure. We believe, as stated by Feiz-Erfan et al.,¹⁸ that this palliative technique is not effective in controlling gelastic seizures, and therefore has a very limited role in the treatment of patients with HH-associated gelastic seizures.

Frontal or Temporal Corticectomy

Seizure semiology generally evolves over time in patients with sessile HHs. A slow spike and wave pattern on

scalp electroencephalograms, which is not uncommonly seen, is often related to development of focal motor features, autonomic phenomena, and secondary generalization including drop attacks. Some seizure types suggest that onset of seizures is in the temporal or frontal lobe. However, even in patients with depth electrode recording showing early involvement of the temporal or frontal region, resection of these cortical areas has invariably failed to control the seizures.¹¹ Clearly the intrinsically epileptogenic hamartoma has to be addressed to achieve a good outcome.

Corpus Callosotomy

Corpus callosotomy is an effective palliative treatment for incapacitating generalized seizures including drop attacks. Unfortunately, anterior callosotomy had minimal benefit in improving the generalized seizure pattern in the 3 patients with HH who were so treated.^{11,50} Thus, like VNS therapy, there appears to be a very limited role for corpus callosotomy in the management of disease in patients with HHs and disabling seizures.

Combined/Staged Approaches and Repeat Surgery

Patients with HH who have a catastrophic epileptic syndrome clearly benefit from neurosurgical treatment. As noted earlier, seizure freedom as well as improvement in both behavioral and neurocognitive deficits occurs in a significant number of patients following initial intervention. However, if disabling seizures persist or if behavior and cognition continue to decline, further medical management options remain limited. It is therefore essential to reevaluate patients with suboptimal results after initial surgery and determine if they could benefit from additional intervention. The Barrow group recently reviewed their experience with repeat surgery in 21 patients in whom the initial procedure failed.⁵⁵ They noted that 14 patients had a > 50% reduction in seizures following reoperation, with minimal additional morbidity. Treatment options at second surgery can include any of the aforementioned approaches.

Conclusions

The treatment of HHs has evolved considerably over the past 2 decades. With proper understanding of the intrinsic epileptogenesis of the hamartoma, elegant approaches were developed, including microsurgical resection and/or disconnection. These techniques, directly targeting the HH itself, have yielded impressive surgical outcomes. Less invasive treatment modalities in which SRS was used have also been shown to have good outcomes in seizure control and improvements in behavior, cognition, and overall development. Younger patients in particular may benefit most from aggressive surgical management in an attempt to curtail or eliminate the behavioral and cognitive sequelae commonly associated with this debilitating subcortical epileptic syndrome. No single neurosurgical approach is likely to treat all forms of HH effectively. Rather, the precise surgical method must be carefully chosen based on important clinical and

radiographic parameters. Occasionally, a multimodal or staged procedure must be used to address the lesion adequately. Indeed, a tailored approach based on patient age, size of the lesion, its attachment to the hypothalamus, and the experience of the treating physicians will provide the greatest likelihood of successful outcome.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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