Although uncommon, the hypothalamic hamartoma (HH) is often associated with a devastating clinical syndrome, which may include refractory epilepsy, progressive cognitive decline, and deterioration in behavioral and psychiatric functioning. Contrary to conventional thinking which attributed seizure origin to cortical structures, the hamartoma itself has now been firmly established as the site of intrinsic epileptogenesis for the gelastic seizures (ie, characterized by unusual mirth) peculiar to this disorder. It also appears that the HH contributes to a process of secondary epileptogenesis, with eventual cortical seizure onset of multiple types in some patients. Anticonvulsant medications are known to be poorly effective in this disorder. Treatment, including some innovative approaches to surgical resection, is now targeted directly at the HH itself, with impressive results. Younger patients, in particular, may avoid the deteriorating course described earlier. Access to tissue from larger numbers of patients at single or collaborating centers specializing in HH surgery will allow for research into the fundamental mechanisms producing this little understood disorder. Refractory epilepsy associated with HH is the premier human model for subcortical epilepsy and an excellent model for secondary epileptogenesis and epileptic encephalopathy.

Semin Pediatr Neurol 12:119-131 © 2005 Elsevier Inc. All rights reserved.

**KEYWORDS** hypothalamic hamartoma, epilepsy, secondary epileptogenesis, epilepsy surgery

Hypothalamic hamartomas (HHs) are rare. Many pediatric neurologists may encounter only a patient or 2 with HH throughout their careers. Prevalence estimates range as high as 1 in 50,000 to 100,000, although the source for this numerical estimate is not provided. The true prevalence of HH is unknown. However, based on our own clinical experience, it is clear that many HH patients have lesions that are missed on initial brain imaging, even when studied with magnetic resonance imaging (MRI). Ongoing technological improvements with MRI, and a heightened awareness of the need to include the hypothalamus as a structure of interest in patients with epilepsy, should decrease the number of cases missed on initial workup. We suspect that HH may be particularly underdiagnosed in the adult population of patients with severe epileptic encephalopathy, specifically in those who obtained imaging performed many years earlier.

Gelastic (ie, laughing) seizures represent one of the hallmark features of HH. Pathological laughter resulting from organic brain disease may have been described as early as 1877 by Trousseau. Subsequent early reports provided localization for pathological laughter to the region of the hypothalamus and floor of the third ventricle. Daly and Mulder first used the term gelastic seizure in 1957, and List et al provided the first definitive report linking gelastic seizures and HHs in 1958. Severely affected patients with HH exhibit a number of additional neuropsychiatric features, including worsening of the epilepsy with multiple seizure types, cognitive decline, and disabling psychiatric symptoms. Although now well recognized, the first authoritative report to fully delineate the HH syndrome was published by Berkovic et al in 1988. Before the 1990s, much of the published literature on HH and epilepsy consisted of small series or individual case reports. Over the past 10 to 15 years, published studies have included ever larger series of patients, and a clearer picture of the natural history (and treatment possibilities) has emerged. A relatively recent case series and review by Nguyen et al included an analysis of 277 previously published cases.
To properly understand the HH syndrome, a distinction must first be made between the 2 different anatomic subtypes. The first subtype consists of HH lesions whose base of attachment within the third ventricle is either partial or complete. These lesions vary significantly in size but typically extend into the third ventricle itself and distort local anatomic structures, most importantly, the fornix or mammillary body.9 This subtype is referred to as the intrahypothalamic (or sessile) subtype (Fig. 1) and is highly associated with neurological features, including an initial presentation with gelastic seizures.10-14 A sizable minority (perhaps 40% or so9) will develop central precocious puberty at some point during their clinical course. Conversely, the second subtype, referred to as the parahypothalamic (or pedunculated) subtype (Fig. 2), is very often associated with central precocious puberty as the presenting abnormality and is uncommonly associated with neurologic problems such as epilepsy or neurodevelopmental problems. Previous studies are in agreement regarding the anatomic and clinical dichotomy characterizing the 2 subtypes.10-14 Most cases can be easily classified into 1 category or the other, but some intermediate forms do in fact exist. For example, some intrahypothalamic forms of HH can be quite large, extending well down into the interpeduncular cistern, and having a base of attachment that includes the underside of the hypothalamus (Fig. 3). Unless otherwise noted, this review will focus on the intrahypothalamic subtype and its associated neurologic problems.

Natural History

The clinical triad traditionally comprising the HH syndrome includes epilepsy, developmental retardation, and central precocious puberty. As mentioned earlier, these features usually segregate into 2 subtypes. However, even within the intrahypothalamic subtype, a great deal of variability exists with respect to the severity and evolution of neurologic features.13 Published case series originating from epilepsy referral centers certainly include ascertainment bias. Even so, exposure to a significant number of these patients makes the variability quickly apparent in our series (>60 patients undergoing surgical resection, as yet unpublished) as well as in others.10 As such, clinical decision making must be highly individualized to each particular patient.

Gelastic Seizures

Gelastic seizures are the most specific identifying feature associated with HH. They are usually quite brief, typically lasting less than 30 seconds, and often being just a few seconds in duration. They can be associated with little or no change in consciousness, particularly early in the clinical course. However, these seizures can be very frequent, occurring up to multiple times per hour in the most severely affected patients. Although superficially resembling laughter, the patients generally do not experience a subjective sensation of mirth, and most family members will quickly learn to distinguish the gelastic seizures from true laughter. Not uncommonly, patients may have clinical events that more closely resemble...
and 10 years of age.\textsuperscript{7} Multiple seizure types have been reported. A meta-analysis of seizure types in published reports is not feasible given methodological differences inherent in these studies, as well as a lack of consistent terminology, particularly in defining seizure type.\textsuperscript{15,20-23} However, these reports collectively suggest the following: complex partial seizures (often described as the “temporal lobe type”) occur in 50% to 60% of HH patients at some time during their clinical course, tonic-clonic seizures (either primary or secondarily generalized) 40% to 60%, atypical absence 40% to 50%, tonic seizures 15% to 35%, and “drop attacks” 30% to 50%. Mullati et al\textsuperscript{21} reported 2 to 5 seizure types for each patient with childhood-onset epilepsy caused by HH. With the caveat that such studies arise from epilepsy referral centers and therefore include ascertainment bias, there is a general consensus in the literature that seizures associated with HH are usually refractory to management with anticonvulsant medications.\textsuperscript{8,15,24}

Because deterioration in the type and severity of epileptic seizures is noted in HH patients, progressive worsening of the interictal electroencephalogram (EEG) is observed as well. The interictal EEG can frequently be normal early in the course of the illness, at a time when gelastic seizures may be the only seizure type.\textsuperscript{19,20,21} The emergence and progressive evolution of abnormal EEG findings generally parallels the course of clinical seizure activity.\textsuperscript{7,20,21} In Tassinari’s review, these “later” interictal EEG studies showed normal results in 2%, generalized spike or spike-wave findings in 47%, multifocal independent spikes in 18%, and focal spikes (temporal\textgreater frontal) in 33%.\textsuperscript{20}

Freeman et al\textsuperscript{25} have recently emphasized the presence of a symptomatic generalized epilepsy phenotype in 12 of 20 patients undergoing HH resection. This subgroup showed features of Lennox-Gastaut syndrome, including the presence of tonic seizures, and slow spike-wave and polyspike morphologies on interictal EEG. Seizure onset (gelastic seizures in 11 of 12) began between birth and 24 months of age (mean, 3 months), whereas tonic seizures developed between 2 months and 9 years of age (mean, 6 years). In summary, the natural history for the development of other seizure types in epilepsy associated with HH is consistent with a process of secondary epileptogenesis.

Cognition and Behavior
Progression of epilepsy severity and interictal EEG abnormalities can also be accompanied by cognitive decline and worsening psychiatric impairment.\textsuperscript{7,15,24,26-28} There is a great deal of individual variability in this regard, but roughly 50% of patients with intrahypothalamic HH, associated with early childhood-onset epilepsy, show this deteriorating clinical course.\textsuperscript{8} The degree of impairment showed by an individual patient can therefore evolve over time. Few studies are available that document this deterioration in the same patient in a longitudinal fashion, but available case studies are compelling.\textsuperscript{28,29}

Cognitive impairment is common in HH patients, with or without the superimposed cognitive deterioration noted ear-
limer, occurring in 80% or more of the patients with the intrahypothalamic subtype of HH. Cognitive problems correlate with the presence of epilepsy as a comorbid feature (patients with parahypothalamic HH lesions typically do not have epilepsy and likewise have little or no cognitive impairment), and also have a positive correlation with an earlier age of seizure onset.

Frattali et al reported detailed findings on 8 patients with epilepsy and HH studied between 4 years 11 months and 13 years 8 months of age. Of the 8 patients, all had onset of gelastic seizures during the first year of life (6 of 8 during the neonatal period). All had daily gelastic and complex partial seizures at the time of study, whereas other seizure types were relatively infrequent. A neuropsychological test battery demonstrated cognitive deficits in all patients, ranging from mild to severe. For the whole group, relative weaknesses were determined in the areas of long-term retrieval and processing speed, with relative strength in the area of visual processing. Language impairments were also shown, with 5 of 7 children performing below age-related norms for initial-letter word fluency. Among the 8 patients, lower scores on a broad cognitive ability scale correlated with higher seizure frequencies for gelastic and complex partial seizures. Although there is a consensus that the concurrence of HH and epilepsy is associated with cognitive and school-related problems, further research into the specifics of the neuropsychological deficits and changes over time are needed.

Patients with epilepsy and intrahypothalamic HH lesions also show a very high likelihood for serious behavioral and psychiatric problems. These can be very disabling and often represent the most significant day-to-day challenge for the family. This has certainly been confirmed in our own series. Problems with mood lability and rage attacks are easily the most prominent, and disabling, features. Patients have poor frustration tolerance, with acting-out behavior and excessive reactivity to relatively minor stimuli, sometimes with destructive and aggressive features.

Weissenberger et al (representing the same research group as Frattali et al) reported on the psychiatric comorbidity in 12 patients with HH and epilepsy. All patients had HH and medically refractory epilepsy and were between the ages of 3 years and 14 years at the time of study. Patients were assessed by structured interview and compared with their closest sibling to control for psychosocial factors unrelated to the HH or seizure disorder. Behavioral problems consisting of significant difficulties with rage, aggression, temper tantrums, and other signs of emotional lability were reported by 83% of families. HH patients showed increased likelihood for Diagnostic and Statistical Manual-IV (DSM-IV) diagnoses of oppositional-defiant disorder and attention-deficit/hyperactivity disorder in comparison to their sibling controls. Interestingly, 17% of the sibling control group was determined to have anxiety symptoms, potentially reflecting the situational levels of stress for these families.

There is a strong association between the comorbid difficulties of refractory epilepsy, cognitive impairment, and behavioral disturbance. Additionally, at least in a significant subgroup of patients with the intrahypothalamic subtype of HH, there is an abundant descriptive literature suggesting that the development of worsening seizures, cognitive decline, and behavioral deterioration occurs simultaneously. This information, taken together with reports describing postoperative clinical improvement, which is discussed later, suggest that the intrahypothalamic subtype of HH is an excellent human model for epileptic encephalopathy.

**Pallister-Hall Syndrome**

Most patients with HH have a sporadic form of the disease, without family history or risk of recurrence and without associated congenital anomalies. However, roughly 5% of the population with the intrahypothalamic subtype of HH have Pallister-Hall syndrome (our series), which can include anomalies such as postradial polydactyly, bifid epiglottis, and imperforate anus. Pallister-Hall syndrome is an autosomal dominant disease, fully penetrant but with variable expressivity, and a high new mutation rate. It is important to recognize this condition to provide proper genetic counseling. Moreover, Pallister-Hall syndrome is important because of our understanding of its molecular pathogenesis and what it might teach us about the sporadic HH cases.

Pallister-Hall syndrome is caused by genomic mutations in the Gli3 gene, a zinc-finger transcription factor in the sonic hedgehog intracellular signaling pathway. Although detailed discussion of this issue is beyond the scope of this article, it is possible that this knowledge may offer a clue to the pathogenesis of the sporadic HH lesion. A single sporadic HH case with a somatic mutation in Gli3 shown in HH tissue but not in blood has been reported by Freeman et al in abstract form.

**Hypothalamic Hamartoma: Intrinsic Epileptogenesis**

A major breakthrough in our understanding of the epilepsy associated with HH was the discovery that the hamartoma itself is intrinsically epileptogenic. This finding was counterintuitive because it had been assumed that partial seizures arise exclusively from cortical structures. Indeed, ictal monitoring of complex partial seizure events in patients with HH, using scalp electrodes or even intracranial electrodes with electrode placement not including the HH itself, suggested consistent cortical onset in some patients, who then subsequently underwent resective surgery of temporal or frontal lobe tissue. As reported by Cascino et al and consistent with our own experience in the early 1990s, the outcome based on this interventional approach was universally poor.

Although based on a relatively small number of patients, there is now compelling direct evidence that ictal events, specifically gelastic seizures, arise from the HH itself. Munari et al reported in 1995 that if ictal video EEG recordings included intracranial monitoring with an electrode placed within the HH, the ictal rhythm associated with gelastic seizures was seen to arise from the HH. This has subsequently been confirmed by multiple other investigators. In addition, electrical stimulation of the depth wire and electrode
contacts into the HH lesion provoked the habitual gelastic (or dacrystic) seizures in some of these same patients.40,41,42 EEG source analysis of interictal spike activity was performed in 4 HH patients with gelastic seizures.43 This showed consistent localization of the early components of spike activation in subcortical regions in the neighborhood of the HH. Later components of the spike transient localized to secondary generators in neocortical regions, most frequently frontal and temporal areas.

Functional imaging with single-photon emission computed tomography (SPECT) has also contributed to our understanding of intrinsic epileptogenesis by showing increased perfusion in the HH with ictal SPECT imaging in comparison to interictal studies.39,44 Kuzniecky et al39 performed ictal SPECT in 3 cases with injection of 99mTc-HMPAO within 5 seconds of onset of gelastic seizures. All 3 patients showed hypothalamic activation, corresponding to the region of the HH by coregistration with structural imaging, as well as activation of the thalamus but without activation of cerebral cortex. Coactivation of the thalamus is consistent with seizure propagation to the anterior nucleus of the thalamus via the mamillothalamic tract.

The most important “proof of concept” for intrinsic epileptogenesis of HH is that gelastic seizures disappear with complete surgical resection (or treatment with other tissue-destructive therapeutic modalities). Treatment results will be discussed in detail later, but ample evidence is now available that seizure control is indeed improved with surgical resection. Although basic mechanisms of pathogenesis and epileptogenesis remain poorly understood, gelastic seizures associated with HH is the best characterized human model for subcortical epilepsy45 and deserves increased recognition as a catastrophic epilepsy syndrome of childhood.46

**Secondary Epileptogenesis**

Unfortunately, this relatively simple (albeit counterintuitive) model of ictal onset from within the HH is not static. As discussed by Dudek and Spitz49 and others, there are 3 key clinical characteristics of secondary epileptogenesis. These are (1) a temporal latency between the onset of seizure activity arising from the primary focus and the onset of seizures from the secondary focus, (2) the secondary focus is anatomically or functionally related, and (3) the secondary focus eventually becomes independent with respect to intrinsic epileptogenicity. Human models obviously do not allow for a direct experimental approach for determining a causal relationship, and, unfortunately, there is no animal model for epilepsy and hypothalamic hamartoma. However, the circumstantial evidence strongly supports the premise that patients with epilepsy and HH often undergo a process of secondary epileptogenesis.52

With regard to these 3 criteria, we have already established that patients with HH may start off with normal background EEGs and exclusively gelastic seizures and that later they can develop mixed seizure types and highly abnormal background EEG patterns with focal, multifocal, or generalized epileptiform discharges. Consequently, the required temporal relationship appears to hold.

The second requirement for anatomic connectivity also appears potentially valid, although confirmatory evidence showing these relationships at a microscopic level in patients with HH is lacking. The intrahypothalamic HH lesions are in close anatomic proximity to the columns of the fornix, mammillary bodies, and mamillothalamic tracts (Fig. 4) and often physically distort the normal position of these structures.42,43 Ictal SPECT studies showing simultaneous activation (increased perfusion) of the HH and thalamus supports the concept that the HH “plugs into” the limbic circuitry of Pa-pez.39,50 Animal studies and preliminary investigations in humans have shown the importance of the mammillary bodies, mamillothalamic tract, and anterior nucleus of the thalamus in epilepsy.31-33 The anterior nucleus, in turn, projects to the cingulate gyrus and then widely to the frontal lobes.56 Alternatively, ictal spread may be mediated by hypothalamic-amygdala connections57 or, via the fornices, to reach mesial temporal lobe structures.23,56 Focal spikes on EEG in seizure patients with HH tend to localize to temporal and frontal regions.23

Lastly, there is compelling evidence, based on intracranial ictal video EEG recordings and intracranial intraoperative recordings, that some seizure types developing later in the course of the disease do not arise from the HH.25,38,42,55 A case report by Munari et al38 serves to illustrate this point. They studied a 16-year-old girl with a history of gelastic seizures at age 30 months. Her interictal EEG initially showed mild background slowing only. Anticonvulsant medications were ineffective. She later developed atonic seizures, coincident with cognitive decline and increasing behavioral problems. An intrahypothalamic HH was discovered on MRI at age 13.
years. EEG at this time showed generalized slowing of background, right and left independent polyspike and runs of slow spike-wave activity. Presurgical evaluation included depth electrode placement into the HH, as well as the frontal and temporal lobes. Gelastic seizures showed ictal onset with a low-voltage fast pattern in the HH itself. However, her atonic seizures showed ictal activity diffusely but not involving the HH contacts. In this case, the normal position of these tracts is not distorted because of the small size of the lesion.

The “Running-Down” Phenomenon

Ultimately, the process of secondary epileptogenesis requires that the secondary seizure focus becomes independent, capable of generating seizure activity on its own, without continuing influence from the original inciting cause. Fortunately, this appears to be a delayed process, and consequently the seizure activity arising from the second focus may be dependent for a period of time on the continuing influence of the inciting epileptogenic region.\(^{21}\)

Using this model, some patients with HH and epilepsy, having developed seizures from neocortical regions because of a process of secondary epileptogenesis, would have reversal and eventual disappearance of the seizures from the secondary site with removal of the HH. In these patients, the second focus is still dependent on the presence, and possibly the seizure activity, of the HH. However, other patients (presumably those further advanced down the pathway of secondary epileptogenesis) would have developed completely independent neocortical seizure foci, and removal of the HH would have no impact on the seizures arising from these neocortical regions.

Multiple reports have documented the improvement of patients with successful resection of HH. Improvement in seizure control includes the gelastic seizures, which are known to arise directly from the HH, and complex partial and secondarily generalized seizures, which spread from the HH. These seizure types often disappear immediately with successful surgery. However, seizures arising from the secondary neocortical foci, either partial or generalized at onset, can improve as well. These seizure types may show a delayed improvement, consistent with a “running down” process or a reversal of a “not-yet-permanent” state of secondary epileptogenesis.

This issue has been directly addressed in a recent publication by Freeman and colleagues.\(^{25}\) They studied 12 children, ages 4 to 17 years, with the intrahypothalamic form of HH associated with features of symptomatic generalized epilepsy. All patients had multiple seizure types, including tonic seizures, and all had EEG abnormalities that included slow spike-wave features (<2.5 Hz). These patients were selected from a larger population of patients with HH and epilepsy.

Seven of these patients underwent intraoperative EEG study as part of their operative plan for resective surgery, with a depth electrode placed into the substance of the HH under direct visualization and additional strip electrodes placed over exposed right frontal cortex. These interictal recordings (under anesthesia) showed no epileptiform abnormality arising from the HH. However, 6 of 7 showed abundant spike-wave activity from the electrodes over frontal cortex.

All patients underwent surgical resection of the HH via the
transcallosal, interforniceal approach. Tonic seizures resolved in 11 of the 12 patients. This occurred immediately in 5 patients but only after a postoperative delay of 1 to 6 months in 6 others. The authors speculate that these 6 cases with delayed postoperative seizure efficacy improved because of a “running-down” process, with reversal of secondary epileptogenesis. Postoperative EEG patterns showed improvement in at least 9 of the 12 patients and eventually complete absence of spike-wave discharges in 5. Improvement in learning, behavior, and quality of life were reported by the families.

Predictive factors for those patients who fail to respond to resective HH surgery have not yet been identified. Our own experience indicates that some patients with a Lennox-Gastaut phenotype, and anatomically complete HH resection, may fail to improve with respect to seizure control, suggesting that the process of secondary epileptogenesis has run its course and reached the stage with permanence of the secondary foci. The implication is that earlier surgery can offer a superior outcome by avoiding the permanently independent phase of secondary epileptogenesis. However, the available evidence does not yet support a firm conclusion. Most importantly, we have not yet identified predictive markers for children who will undergo deteriorating course because of secondary epileptogenesis (and its associated epileptic encephalopathy) from those who will not.

**Treatment**

There are no controlled or comparative treatment trials for HH and its associated epilepsy. The fact that most centers see few HH patients because of the relative rarity of the condition invariably means that most reports have included only a small number of cases. More recently, some larger open-label series describing results of therapeutic interventions have been published.

**Anticonvulsant Medications**

There are no studies directly addressing the issue of medical management in patients with HH and epilepsy. However, there is broad consensus in the published literature about the lack of efficacy of anticonvulsant medications. In contrast, a small number of cases responsive to medical management have been detailed. It is likely that the published literature underestimates the number of medication-responsive patients, reflecting the ascertainment bias of epilepsy referral centers. However, probably <5% of patients with intrahypothalamic HH and epilepsy achieve complete and sustained seizure control with medications alone. Medications are often described as lacking efficacy against gelastic seizures. Nevertheless, these same medications may ameliorate the partial seizures resulting from secondary spread or the generalized seizures associated with HH and therefore have value in patient management.

**Vagus Nerve Stimulation and Ketogenic Diet**

The use of vagus nerve stimulation (VNS) has been described in a small series of patients with HH and epilepsy. In this series of 6 patients, 1 had a 90% reduction in seizure frequency and 1 a 50% reduction. The others showed no clinically significant improvement in their seizures. However, 4 of the 6 were described as having severe autistic behaviors that improved with VNS.

We are not aware of any reports detailing the use of the ketogenic diet in patients with HH and epilepsy. Palmini et al referred to 2 patients who “improved” with ketogenic diet treatment after failing 2 resective procedures targeting the HH.

**Surgical Resection**

The earliest resective procedures were performed on patients with the pedunculated subtype of HH and precocious puberty. These patients usually do not have epilepsy or cognitive disturbance and are now treated medically with gonadotropin-releasing hormone agonists. Accordingly, surgical resection is infrequently required for this subgroup.

Before the recognition that the HH itself was intrinsically epileptogenic, resective surgery for HH associated with epilepsy was discouraged. However, even some of the earliest case reports of resective surgery for patients with precocious puberty included children with gelastic seizures, with clinical improvement. Early efforts at HH resection (specifically for the epilepsy) yielded encouraging results for seizure control and even reversal of cognitive and behavioral decline. The possibility that the HH itself may be intrinsically epileptogenic seems to have been proposed as early as 1983.

Nguyen and coworkers recently presented a meta-analysis of all published reports of surgical resection in patients with HH and seizures. They discovered 71 procedures directed at the hamartoma (66 HH resections and 5 radiofrequency thermoablations), with 15 describing removal of 95% to 100% of the lesion and 37 describing partial resections. Of the 15 with complete or near-complete resections, 10 (66%) were seizure free and 5 (33%) had “significant improvement.” Less impressive results were seen in those undergoing partial resection.

Not surprisingly, resective surgery of intrahypothalamic hamartomas is associated with significant risk. Decisions about proceeding with a more invasive treatment approach must always be highly individualized. For infants and young children with exclusively gelastic seizures, a decision to observe and not intervene surgically may be the most comfortable decision for some families. However, the observation that 50% of such patients will develop the deteriorating form of the syndrome and that 75% to 100% will develop other seizure types must be recognized. In light of recent developments in surgical techniques, our bias is for earlier surgery to avoid the deteriorating course. Further research into the cognitive and psychiatric outcomes with early surgery, later sur-
gery, and no surgery is required to guide these difficult clinical decisions.

**HH Classification and Surgical Anatomy**

Having established that surgical resection of the HH can be an effective treatment and that medications are not, let us now turn to a brief discussion of surgical anatomy and surgical approach. We have already seen that there is a significant difference in the clinical phenotype between HH lesions arising (at least in part) from the walls of the third ventricle (the intrahypothalamic type in this report) and those lesions that are connected to the tuber cinereum or inferior aspect of the third ventricle by a pedunculated stalk. A number of authors have proposed classification schemes for HH lesions, including Boyko et al\(^{10}\) and Debeneix et al\(^{13}\) (pedunculated type and sessile type), Valdueza et al\(^{21}\) (subtypes Ia, Ib, IIa, IIb), Arita et al\(^{12}\) (parahypothalamic type and intrahypothalamic type), and Fohlen et al\(^{62}\) and Delalande and Fohlen\(^{70}\) (types I-IV). Our experience with a large number of patients suggests that there is a relatively smooth continuum between these subtypes and that there is a substantial amount of interobserver variability in terms of assigning subtypes to intermediate cases. Although the merits of one classification scheme over another are debatable, each of these schemes addresses an important common theme: the surgical anatomy of the HH lesion.

A number of different surgical approaches have been developed and advocated for resection of HH lesions. It now appears increasingly clear that the surgeon can and should choose from among these approaches based on the specific anatomic features of each HH lesion.\(^{62,76-79}\) Most importantly, this concerns the size and location of the base of attachment. The majority of HH lesions are attached predominantly to 1 side of the hypothalamus or the other.\(^{9}\) Simply stated, lesions that attach within the third ventricle and that have a vertical plane of attachment should usually be approached from above, that is, superiorly through the third ventricle. Lesions attached to the inferior surface of the hypothalamus and having a horizontal plane of attachment should be approached from below. Intermediate HH lesions, often larger masses with both intraventricular and parahypothalamic planes of attachment, may require a staged (or simultaneous) resection using both approaches.

**Surgical Approach: From Below**

Until relatively recently, resective surgery for HH was always performed with a surgical approach from below. As reported by Nishio et al\(^{74,80}\) and Machado et al\(^{29}\) in detailed case studies, resection of the HH via a pterional approach had the potential to control seizures and improve the patients cognitive and behavioral level of functioning. Other variations on this theme have also been described, including orbitozygomatic\(^{70}\) and subfrontal approaches.\(^{30}\) A small number of cases have been approached through the lamina terminalis\(^{81-83}\) (technically, a more anterior, rather than inferior approach, but we are including these cases in the “from below” group because of the limited number).

The advantage of approaching HH lesions from below includes a shorter distance. However, these approaches traverse territory with important vascular structures, including the internal carotid artery, posterior communicating artery, and associated perforating branches. The optic tracts and chiasm and the third cranial nerve are also vulnerable.\(^{77}\) Even so, surgical series of patients undergoing resection of pedunculated HH lesions report excellent results with a low rate of complications.\(^{12,13,83}\) These lesions typically have a relatively narrow base of attachment, and the approach from below offers optimal direct visualization.

On the other hand, surgical resection of the intrahypothalamic subtype of HH from below is less successful and arguably has a higher complication rate, in comparison to surgical approaches from above.\(^{77,84}\) Palmini et al\(^{30}\) reported a representative series in this regard, with 13 patients with HH and epilepsy from multiple centers. All patients had multiple seizure types, cognitive impairment, and behavioral disorders, and 12 of 13 had HH lesions with intrahypothalamic attachment. Complete resection was achieved in 2, subtotal resection in 7, and partial resection in 4. Five of the patients underwent a second surgical intervention. After the first surgery, 2 patients (15%) were seizure free and 6 (46%) were significantly improved with >90% improvement in seizure frequency or complete control of all noneplectual seizures. The patients with partial resection were least likely to improve. Some additional improvements were seen with a second operation.

Complications in this series included ischemic stroke affecting the thalamus and/or internal capsule in 4 (31%), most with good recovery, and injury to the third cranial nerve in 4 (31%), with complete recovery in 3. One patient had transient syndrome of inappropriate antidiuretic hormone secretion (SIADH), and 1 had a persistent increase in appetite.

**Surgical Approach: From Above**

Rosenfeld et al\(^{61,78}\) were the first to use the transcallosal, anterior interfornical (TAIF) approach to the third ventricle to resect intrahypothalamic HH in patients with refractory epilepsy. This approach, using microsurgical technique and intracranial guidance systems, allows for excellent direct visualization of the HH and its base of attachment within the third ventricle (Fig. 5). Rosenfeld’s modification of the transcallosal approach to the third ventricle with a more anterior, transseptal trajectory minimizes retraction of the columns of the fornix and also avoids the likelihood of injury to the internal cerebral veins located more posteriorly.

Harvey et al\(^{28}\) recently presented follow-up data on 29 consecutive patients undergoing intrahypothalamic HH resection via the TAIF approach, all operated on by Rosenfeld in Melbourne, Australia. Age at surgery ranged from 4 to 23 years (mean age, 10 years), and all had a history for gelastic seizures at some point during their clinical course. All patients had additional seizure types, including a symptomatic generalized epilepsy phenotype in 19 (66%). Coexisting
morbidities included central precocious puberty in 13 (45%), intellectual disability in 21 (72%), and behavioral problems, most frequently rage and aggression, in 18 (62%). At least 95% resection of HH lesion volume was achieved in 18 patients (62%) and 75% to 95% resection in 7 patients (24%). Of the latter, 4 had complete or near-complete disconnection of the lesion from its base of attachment. Postoperative follow-up with a minimum of 12 months showed 15 patients that were completely seizure free (52%) and 7 patients (24%) with at least a 90% improvement in seizure frequency. Attention and behavior were improved in many patients, but further details were not provided.

Small, unilateral ischemic strokes of the thalamus and internal capsule occurred in 2 cases (7%), both with eventual complete recovery. Transient third cranial nerve injury was reported in 1 patient (also 1 of the patients with stroke). Postoperative endocrine issues included need for thyroid replacement therapy in 5 (17%). The majority of patients (55%) developed mild, asymptomatic hypernatremia in the immediate postoperative period, but no patients had persistent SIADH. Increased appetite with weight gain was reported in 45% of patients but resolved in half of these with time.

Impairment of short-term memory is a major concern because the TAIF procedure, despite its more anterior trajectory, still requires some degree of separation and retraction of the columns of the fornix. Short-term memory disturbance was noted in 14 patients (48%) in the postoperative period but resolved in most. Residual impairment of short-term memory was described in 4 patients (14%). The transcalsosal, interforniceal approach is now recommended for patients with the intrahypothalamic subtype of HH and epilepsy.

Disconnection and Endoscopic Resection

Fohlen et al62 and Delalande and Fohlen76 have recently introduced endoscopic resection/disconnection of the intrahypothalamic subtype of HH as an additional option. The premise is that a surgical procedure that completely disconnects the HH lesion is equally effective as surgery with complete resection. A series of 18 patients is reported, with 1 patient undergoing complete resection and 17 undergoing a disconnection procedure, either with open craniotomy (pterional approach) as the initial procedure in 14 or disconnection via an endoscope as the initial procedure in 3 and as a second procedure in 7. Seizure efficacy for the whole group (after 1 procedure in 10 patients and 2 procedures in 8) showed that 9 (50%) were seizure free and 9 (50%) were significantly improved (Engel class II or III). Complications included 2 patients with ischemic stroke, 1 with postoperative meningitis, transient SIADH in 2, and residual panhypopituitarism in 2.

Akai et al87 also reported a case advocating endoscopic surgery for HH as a less invasive alternative. Our center has surgically treated over 20 patients with HH and epilepsy over the past year with a transventricular, endoscopic resection (Figs. 6 and 7). Follow-up at present is short term, but the results have been encouraging.68 Although endoscopic resection clearly results in a faster postoperative recovery,62 a determination of the relative merits of endoscopic HH resection versus open resection with the TAIF approach requires comparison of long-term outcomes.

Stereotactic Radiosurgery (Gamma Knife)

The gamma knife (GK) has also been investigated as an ablative or destructive therapy for HH lesions.30,63,87,90-91 The ap-
peal of GK is that it is noninvasive and can deliver a “killing” dose to a small volume of tissue, with little or no injury to surrounding brain. Limitations in its use in the hypothalamus include the need to avoid damage to the optic tracts, which are known to be relatively radiosensitive, and the large size of some HH lesions. There is also a significant lag in the emergence of a beneficial effect relative to the time of delivery, from 3 to 12 months or even longer.

Regis et al\textsuperscript{63} described a series of 10 patients with the intrahypothalamic subtype of HH and refractory seizures treated with GK at 7 different centers. Four patients became seizure free (40%), 2 after a second course of GK treatment. All remaining patients also improved to a variable degree. Poikilothermia in 1 patient was described as the only adverse event. Optimal dosimetry remains to be established, but this report showed favorable results in patients receiving at least 17 Gy to the margin of attachment of the HH lesion. GK is a viable treatment option for many patients with HH and epilepsy. Further study to define optimal use of GK compared with other treatment modalities is required.

**Additional Treatment Strategies**

Stereotactic radiofrequency thermoablation has been described in a relatively small number of patients.\textsuperscript{21,39,41,64,92,93} This technique involves stereotactic placement of a depth wire into the HH target and then causing a destructive thermal lesion by physically heating the probe tip. Most of these publications are single case reports.

Kuzniecky and Guthrie\textsuperscript{64} recently reported a series of 12 patients treated with this modality, 8 with stereotactic thermoablation alone and 4 with endoscopic resection followed by thermoablation. In the first group of 8, 3 (38%) were seizure free and 2 (25%) were at least 90% improved with respect to seizure frequency. One patient experienced a transient third nerve palsy. In the second group of 4, 2 patients became seizure free and 1 had at least a 90% improvement in seizure frequency. There was 1 death because of brainstem infarction, and 1 patient had transient difficulties with short-term memory. It is of interest that some series on other treatment modalities include patients

**Figure 6** Illustration representing the transventricular, endoscopic approach for resection of HH. The approach is best made through the Foramen of Monro opposite to the base of attachment of the HH. Larger ventricles and adequate navigating room within the third ventricle are relatively favorable factors when considering the transventricular, endoscopic approach. (Reprinted with permission from the Barrow Neurological Institute.) (Color version of figure is available online.)

**Figure 7** Intrahypothalamic subtype of HH, (A) before and (B) after transventricular endoscopic resection. Sagittal T2 FSE TR 3500, TE 83. The patient is an 11-year-old boy with multiple daily gelastic seizures and several complex partial seizures per week. He is mildly delayed but has disabling rage behaviors and attention-deficit/hyperactivity disorder. Note the close physical proximity between the HH and the mamillary bodies. He is seizure free and greatly improved with behavior approximately 6 months after his procedure.
who failed stereotactic thermoablation therapy. (Ster
eoctatic thermoablation should not be singled out in this
gard. Most of the larger series include patients who have
failed other treatment modalities besides medication man-
gagement, including cortical resection, corpus callosotomy,
and VNS.)

Interstitial radiosurgery with stereotactic implantation of
radioactive seeds was described in a series of 7
patients by Schulze-Bonhage and coworkers. The refer-
cence dose was targeted to be 60 Gy at the outer margin of
the HH. Seven patients underwent attempted placement,
and seeds were successfully placed in the HH in 6. Four of
these 6 patients had surgical placement of seeds on at least
2 separate occasions. Two patients are described as seizure
free subsequent to therapy, and two have auras only (Eng-
class II). No complications were noted at 1 year of
follow-up.

Conclusion

There has been tremendous progress in our understanding
of HH over the past 15 years. Although uncommon, the
intrahypothalamic subtype of HH can present as a cata-
strophic epilepsy in early childhood. Many of these pa-
tients will experience a deteriorating course with worsen-
ing of seizures, cognitive functioning, and behavior. We
now know that the HH itself is intrinsically epileptogenic
and surgically treatable. The last few years have clarified
that a surgical approach from above is more effective for
most intrahypothalamic lesions and has led to increasing
enthusiasm about surgical intervention. The potential of
avoiding the process of secondary epileptogenesis and ep-
ileptic encephalopathy with early surgery is suggested by
our current understanding of this disorder. Additional in-
vestigation is required to clarify this critical issue. Epilepsy
associated with HH is an important human model for sub-
cortical epilepsy and secondary epileptogenesis. Learning
more about the basic mechanisms concerning HH and
seizures may provide insights that help our understanding
of other forms of epilepsy.

Acknowledgments

The authors wish to thank Maggie Varland, RN, our coor-
dinator with the Hypothalamic Hamartoma Program at the
Barrow Neurological Institute. We also wish to thank the
Foundation and Women’s Board of the Barrow Neurolog-
ic Institute for their ongoing support of our research
efforts. Finally, we would like to acknowledge the perse-
verance and courage of our HH patients and parents.

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