The evolution of treatment for hypothalamic hamartoma: a personal odyssey

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The prognosis for patients with hypothalamic hamartoma has improved dramatically over the last 20 years, for 3 main reasons. First, because of improved understanding of the anatomy and pathophysiology of these varied lesions. Second, due to advances in brain imaging and refinements in microsurgery, including the anterior transcallosal interforniceal approach, endoscopic, and skull-base approaches. And third, because of increasing experience with stereotactic radiosurgery, interstitial radiotherapy, and radiofrequency lesioning. Patients with hypothalamic hamartoma should be managed in comprehensive epilepsy centers where the treatments are individualized and concentrated in the hands of surgeons who can perform the full range of surgery, including approaches to the third ventricle. Total seizure-freedom rates of 52% to 66% have been achieved with surgery. (DOI: 10.3171/2010.11.FOCUS10244)

Key Words • hypothalamic hamartoma • radiosurgery • gelastic epilepsy

Hypothalamic hamartomas frequently cause intractable epilepsy with frequent gelastic and other mixed seizure types, intellectual disability, appalling behavioral disturbance with severe temper tantrums, and precocious puberty. Resection of the HH may cure the seizures and result in dramatic improvements in behavior, concentration, and the ability to learn new information. These children are given the chance to lead a relatively normal life and their parents are overjoyed to see this transformation in their child. A neurosurgeon could receive no greater reward.

Prior to the development of successful surgery for HH, the prognosis for these children was abysmal because the resulting epilepsy is particularly resistant to antiepileptic drugs and these patients frequently experience a relentlessly deteriorating clinical course. The seizures may occur every few minutes or even virtually continuously in those who are severely affected. This creates an epileptic encephalopathy that results in serious cognitive decline. Formerly, these children eventually became a complete burden on their parents, and family dynamics often became dysfunctional. Many of these children had a shortened lifespan and required institutional care. Successful intervention for these children has evolved, particularly in the last 20 years, and it is the purpose of this review to examine the factors responsible for this transformation. This paper reflects a personal view and does not attempt to exhaustively review and synthesize all the series of patients with HH reported in the literature, but instead attempts to focus on the principal developments in the field as observed from a personal perspective over this extended time period.

Mixed seizure patterns in patients with HH often electrically localize to the cortex. Because of this localization, frontal corticectomies and temporal lobectomies were performed without achieving control of the seizures. We identified examples of these patients in our series. The HH was not always noted on CT, particularly if it was small, and it was only after the introduction of MR imaging that the presence of the HH and its enormous anatomical variations were appreciated in these patients with intractable epilepsy. It is also challenging to diagnose gelastic seizures in infants. Some of these infants may be diagnosed with gastroesophageal reflux or colic. In some patients Lennox-Gastaut syndrome may be due to HH, but misdiagnosed.

The Development of Surgery for HH

Before the mid-1990s there was a legitimate fear of HH surgery because of the location of the hamartoma, the uncertainty that the epilepsy was emanating from the hamartoma, and the chance of hypothalamic damage and serious complications or death caused by surgery to remove the HH. Neurosurgeons were generally reluctant to remove a lesion from the hypothalamus. The first
reports of surgery for HH were those of Northfield and Russell, who described 2 patients in 1967 who underwent subfrontal approaches for precocious puberty. The first lesion was probably pedunculated. The second lesion was 2 cm in diameter and attached to the tuber cinereum. Patients with central precocious puberty usually have pedunculated HHs attached to the infundibulum or tuber cinereum. In the French literature in 1969, Paillas et al. reported the case of a 14-month-old child with epilepsy who underwent 2 operations, the first via a transsylvian approach with removal of the temporal pole, and the second operation a subtamoral approach to excise an HH. Interestingly, these 3 hamartomas were diagnosed using air encephalography.

The literature on HH before the 1990s contained many individual case reports and small series with limited follow-up, and thus there could be no confidence that surgical treatment was regarded as an evidence-based standard. The surgery was often unsuccessful with lower epilepsy control rates compared with other types of epilepsy surgery, and serious complications and deaths were reported. Therefore, very few patients were referred by neurologists to neurosurgeons for surgical treatment.

The reasons for the successful transformation of the treatment of HH were first, improved definition of the exact anatomy and relationships of the HH observed on multiple projections on MR images; second, the realization that the HH was not a significant intrinsic structural element of the hypothalamus, but was a discrete lesion fused to the hypothalamus, which could be safely removed or disconnected in many patients; and third, increasing refinement of microsurgical techniques aided by intraoperative stereotactic navigation. In conjunction with the evolution of the surgery for HH was the increasing application of stereotactic radiosurgery. Further treatment options for HH are radiofrequency lesioning and interstitial radiotherapy with, but the sample sizes reported are smaller and these treatments are not freely available.

It took some time for the realization and proof that the seizures were emanating from the HH itself and rapidly spreading to the cortex. There are multiple possible routes by which seizures spread from the HH into adjacent and remote parts of the brain. One pathway is that the seizures spread directly through the mammillary body to the thalamus and beyond via the mammillothalamic tracts, so that disconnection of the HH from the mammillary body has become one of the key goals of the disconnection surgery. Sessile HHs are attached to one or both mammillary bodies. Hypothalamic hamartoma is a model for human subcortical epilepsy, secondary epileptogenesis, and epileptic encephalopathy. The frequent seizures in these children may cause an epileptic encephalopathy with cognitive and behavioral decline. This encephalopathy tends to resolve following resection or disconnection of the HH. The best results from treatment of the HH will likely result if the treatment occurs before the evolution of the seizure pattern into a widespread secondary generalized epilepsy. Once this secondary epilepsy is established, removal of the HH will not be likely to eliminate the generalized seizures, which may be independently generated in the cortex.

The Royal Children’s Hospital Experience

Hypothalamic hamartoma is a rare, usually sporadic condition that we initially estimated to occur in approximately 1 person per million of the population, based on the number of patients who were referred to Royal Children’s Hospital from within Australia. However, with greater clinical recognition and improved diagnostic capability using MR imaging, the incidence of HH is currently reported to be about 1 in 200,000. Advances in the treatment of patients with HH could not have occurred without a strong multidisciplinary team approach within the setting of a comprehensive epilepsy program, in this case led by the pediatric neurologist Dr. Simon Harvey. These complex patients require an extensive preoperative workup, which has been described previously.

The first patient we operated on for HH and gelastic epilepsy at Royal Children’s Hospital presented in 1996. The exophytic component of the lesion, attached to and extending below the hypothalamus, could be debulked via a subfrontal approach, but a significant component of the lesion was still present within the cavity of the third ventricle and was attached to the medial walls of the hypothalamus on the postoperative MR image. It was clear that an approach from below could never remove this component completely or safely and that epilepsy control would probably remain poor if a significant component of the lesion remained attached to the hypothalamus. A transcallosal approach would enable exposure of this component of the HH and permit excision with what we surmised would result in better control of the epilepsy with acceptable morbidity. The next patient who presented with a sessile intrahypothalamic and intraventricular hamartoma causing intractable epilepsy had the transcallosal approach performed with success. The initial transcallosal experience in 5 patients at the Royal Children’s Hospital resulted in 3 patients who were seizure-free and 2 with only occasional, brief gelastic seizures with reduced antiepileptic drugs. There were marked improvements in behavior, school performance, and quality of life in these 5 patients. Follow-up ranged from 9 to 37 months (mean 24 months).

There was clearly a need for a detailed prospective analysis of a sizable series of patients with HH, including a detailed description of the epilepsy, the type and extent of the surgery, the postoperative course, the endocrine function including risk of diabetes insipidus, thirst center dysregulation, weight and appetite changes, and effects on vision, mood, and behavior. The degree of control of the epilepsy and an adequate length of follow-up were prime concerns. Neuropsychological outcome including memory function were also of interest. Many previous case reports and series had relatively short follow-up durations. We expanded our initial series to 29 cases by 2003; 52% were seizure-free, and 24% had a > 90% reduction in seizure frequency after a mean follow-up of 30 months (range 12–70 months). These results were later replicated at the Barrow Neurological Institute.
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2002, Palmini et al. reported on 13 patients who underwent surgery for HHs from 3 centers, 12 using a fronto-temporal approach and 1 using an endoscopic approach. Delalande and Fohlen reported on 17 patients in 2003 who underwent surgery for HH (14 transsylvian and 9 endoscopic approaches). We subsequently reported our epilepsy findings, endocrine findings, and MR imaging findings. There was a wide variation in the size and position of HH, and the attachments and relations of the HH were also described.

We were able to acquire a relatively large series of patients with this rare condition because the families of these children developed their own website called HHugs (http://www.hhugs.com/) which informed them about what treatments were available around the world along with some analysis of the medical literature, and in doing so empowered them to make decisions about the treatments they wished to pursue. We were surprised when patients came from the United Kingdom, US, Europe, Tanzania, and even Mongolia. This response demonstrates the powerful force-multiplying effect of the internet on the way medicine is now practiced, especially for patients with rare disorders. There are now 250 families who are members on this site.

The goal of surgery is to resect and/or disconnect the hamartoma from the adjacent hypothalamus and to preserve the mammillary bodies (which may be malpositioned and deformed), mammillothalamic tracts, tuber cinereum, and hypothalamic nuclei. The spread of seizures occurs in part via the mammillary body. The surgery should ideally be performed before the onset of secondary generalized epilepsy and has been achieved endoscopically in infants as young as 13 months.

There was concern that the standard transcallosal interforniceal approach would, of necessity, retract and injure both fornices and cause a significant rate of permanent short-term memory disturbance. We therefore refined the standard transcallosal interforniceal approach to a more anterior trajectory with a more restricted access passing between the columns rather than between the bodies and commissure of the fornices where they are close, flattened, and partially fused and where more retraction would occur. Although we could not test the memory and cognitive function of the very young children, the rate of short-term memory deficit in our series was 48.3% (14 of 29 patients) in the early postoperative period, which decreased to 13.8% (4 of 29) in the longer term. It should be noted that that early patients in the series underwent the standard transcallosal approach. Ng et al. reported 3 (8.1%) of 37 patients had permanent short-term memory deficit following endoscopic resection for HH. We believe this disability may be acceptable if the terrible consequences of the HH abate following the surgery.

After the successful anterior interforniceal transcallosal surgery on a 4-year-old boy with HH from Phoenix, Arizona, Dr. Spetzler and Dr. Rekate kindly invited me to demonstrate the technique at the Barrow Neurological Institute. I was also invited to demonstrate this surgery at Shands Hospital, University of Florida, Gainesville; in Singapore; at Radcliffe Infirmary, Oxford, United Kingdom; and at Dana Children’s Hospital, Tel Aviv Medical Center, Israel.

A recommended pathway to refine a surgical technique or approach is to use a fully equipped microsurgical laboratory and dissect cadaver specimens injected to clearly display arteries and veins. I did not have this facility available at the time of refining the transcallosal interforniceal approach, but the anatomy of the more targeted anterior, transcallosal, interforniceal approach could be studied in detail with the support of Dr. Spetzler and Dr. Rekate in the anatomy laboratories of the Barrow Neurological Institute. Dr. Siwanuwat, a Barrow Neurological Institute fellow at the time, conducted the detailed anatomical studies.

The Endoscopic Approach

The endoscopic approach to HH was initially reported in the literature mixed with reports of the open approach. Rekate et al. reported the early outcome of 44 patients with normal-sized ventricles who underwent endoscopic surgery. Fourteen patients had complete endoscopic removal of the HH, and there was total control of seizures in 13 of these patients. This investigative group reported prospectively on the endoscopic approach in 37 consecutive patients with HH. Mean follow-up of these patients was 21 months (range 13–28 months). Twelve patients underwent a complete excision, 18 were seizure-free, and 26 had more than a 90% reduction in seizures. Postoperative stay using this approach was reduced compared with the open transcallosal approach. The complications in this study were short-term memory loss in 3 patients and small thalamic infarcts in 11 patients. Ng et al. concluded that the endoscopic approach is a safe and effective treatment for seizures and is comparable to the transcallosal approach, but recovery time is shorter. Rekate et al. have defined the indications for the endoscopic approach. The ability to approach the HH unilaterally via the foramen of Monro and not disturb the fornix on both sides is an advantage compared with the open midline transcallosal approach.

Discussion

There have been extraordinary advances in scientific knowledge concerning the genetics, histopathology, and ultrastructure of HH, the electrical properties of the neurons in HH, and the molecular correlates of central precocious puberty in HH. These discoveries have advanced our understanding of the pathogenesis and clinical features of HH and informed the treatment of these complex patients.

The advantage of the open transcallosal or transventricular endoscopic approach compared with the skull-base approach is the direct visualization of the HH and its main attachments to the hypothalamus, including the mammillary bodies. A wider angle of view is likely to be obtained with the transcallosal compared with the
endoscopic approach. While it is our opinion that the intrahypothalamic, third ventricular hamartoma should be approached from above, the subfrontal and/or transylvian approach is indicated for primary surgery on HHS in which the lesion is pedunculated or exophytic and parahypothalamic, attached to the base of the hypothalamus extending laterally beyond the floor and the vertical axis of the third ventricle and inferiorly into the basal cisterns. Although the third ventricle may be entered via the lamina terminalis, the view of the entire HH is generally restricted with this approach and there may be problems from frontal lobe retraction and vascular injury. Where the approach from above has not been able to remove or disconnect an inferior extension, the approach from below may also be required at the same session or delayed as a second stage. The orbitozygomatic craniotomy is the preferred approach in these cases because of the minimization of retraction of the brain and the flat-or upward-angle trajectory to the lesion. Abla et al. performed the orbitozygomatic approach in 10 patients and reported 40% of patients were seizure-free, 40% attained > 50% seizure reduction, and 66% attained seizure freedom when there was a total or near-total excision of the HH. Ng et al. found that 100% resection correlated with better seizure control.

Stereotactic radiosurgery has an established and important role in primary and secondary treatment of patients with HH. The epilepsy control rates are not as high as with open surgery. There is also a latency period for the epilepsy control to be achieved. Potential injury to surrounding structures including the optic pathways and chiasm is a concern, but the risk to memory is lower compared with open surgery. We have recently reported a significant risk of memory deficit following transcaval surgery in the older adolescent and adult patients with HH. Therefore, stereotactic radiosurgery may be the preferred treatment option for the older adolescent or adult patients with HH and with intact memory and milder epilepsy, or in select patients with bilateral mammillary body attachment. Stereotactic radiosurgery may also have a role in treating residual HH in patients with ongoing epilepsy.

Treatments offered for patients with HH should be individualized because there is such an enormous range of clinical, electroencephalographic, and radiological features. The epilepsy surgeon should be familiar with the transcaval, endoscopic, and extended skull-base approaches. This surgery is quite different from other types of (pediatric) epilepsy surgery. Stereotactic radiosurgery and other minimally invasive procedures are less intrusive options that should also be considered.

Future research in patients with HH could be directed to improving medical therapy; better defining the ideal age for surgery; better defining the selection of cases for surgery, radiosurgery and other treatments; and the selection of the most efficacious surgical options with the least risk. Reporting detailed long-term follow-up for substantial cohorts of patients with HH will also be of great interest.

Conclusions

It has been a privilege to have experienced the transformation of the treatment of children with HH over the past 20 years, from what was believed to be a virtually untreatable condition to the current situation in which these children have been given a chance to experience a normal life. The best outcomes will be achieved with the management of these patients by an experienced multidisciplinary team in comprehensive epilepsy centers in which there is a sizeable volume of patients in all their variety. The epilepsy surgeon should be well versed in all the approaches to these complex lesions.

Disclosure

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

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