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Surgical management of hypothalamic hamartomas in patients with gelastic epilepsy

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Gelastic epilepsy (GE) associated with hypothalamic hamartomas (HHs) is now a well-characterized clinical syndrome consisting of gelastic seizures starting in infancy, medically refractory seizures with or without the development of multiple seizure types, and behavioral and cognitive decline. It has been postulated that the development of the HH-GE syndrome is a result of a progressive epileptic encephalopathy or secondary epileptogenesis, which is potentially reversible with treatment of the HH. A variety of surgical options for the treatment of HHs exist, including open and endoscopic procedures, radiosurgery, interstitial radiotherapy, and stereotactic radiofrequency thermocoagulation. Surgical treatment can result in seizure freedom in up to 50% of patients and can be accompanied by significant improvements in behavior, cognition, and quality of life. Partial treatment of HHs may be sufficient to reduce seizure frequency and improve behavior and quality of life with less risk. A component of reversible cognitive dysfunction may be present in some patients with an HH-GE syndrome. *(DOI: 10.3171/FOC/2008/25/9/E8)*

Key Words • epilepsy surgery • gelastic epilepsy • hypothalamic hamartoma

Gelastic epilepsy associated with HHs is now a well-characterized clinical syndrome consisting of gelastic seizures starting in infancy, which become refractory to medications and progress to include the development of multiple seizure types in association with severe behavioral and developmental decline.[6,7] The HH-GE syndrome was initially believed to be the result of a progressive epileptic encephalopathy[5,6] or, more recently, secondary epileptogenesis.[24] Subsequent confirmation of the intrinsic epileptogenesis of HHs[23,25,29] and, more importantly, their association with gelastic seizures has led to the belief that not only the seizures themselves but the accompanying encephalopathy may be reversible with surgical treatment of the HH. The treatment of HHs through a variety of surgical approaches[1,3,9,13,19,21,22,27,31,35,36,38,41,49,50,54] has demonstrated that seizures can cease and improvement in behavior and cognitive dysfunction is possible, supporting the concept that HHs may be associated with an element of reversible encephalopathy.

Hypothalamic hamartomas are a rare nonneoplastic developmental lesion of the inferior hypothalamus that are composed of cytologically normal neurons, which are abnormally distributed within the hypothalamus.[8] The majority of cases are sporadic, but ~ 5% of cases may be associated with the Pallister-Hall syndrome, which is an autosomal dominant disorder associated with a frameshift mutation in *GLI3*.[7] Hamartomas are found in the hypothalamus, attached to the tuber cinereum or more commonly to one or both mammillary bodies. Microscopically, the abnormally distributed but cytologically normal neurons and glia predominate in a nodular pattern composed of hundreds of small to intermediate-size neurons. The neuronal size suggests that they may be interneurons, which may contribute to the basic intrinsic epileptogenicity of HH.[10]

Abbreviations used in this paper: EEG = electroencephalography; GE = gelastic epilepsy; HH = hypothalamic hamartoma.

Clinical Presentation of HHs

Hypothalamic hamartomas can be identified incidentally, in association with precocious puberty alone or with a syndrome of intractable GE, and in some cases of severe behavioral and intellectual impairment. Gelastic seizures, the initial manifestation of the HHs, often date back to the first years of life,[8,11] although they may not occur until late childhood or even adulthood.[28,52] Seizures typically are characterized by brief episodes of inappropriate laughter possibly followed by facial contractions in the form of a smile or grimace; in the latter case, they have been referred to as "dacrystic seizures" (that is, crying seizures). Autonomic features such as flushing, tachycardia, and changes in respiration can occur with the seizure.[20] The evolution of GE can include multiple seizure types such as generalized tonic-clonic seizures or tonic and atonic seizures as part of a generalized encephalopathy with diffuse EEG changes, intellectual deterioration, and behavioral impairment characterized by difficulty controlling anger outbursts or "rage attacks."[6,57]

Patient Evaluations

Magnetic Resonance Imaging

High-resolution MR imaging remains the procedure of choice for identifying HHs, which may be as small as a few millimeters to a few centimeters in size. Hamartomas are usually isointense to gray matter on T1-weighted imaging and hyperintense or isointense on T2-weighted imaging and do not enhance after Gd administration. The hamartomas can be "pedunculated"[56] or "parahypothalamic";[3] that is, the hamartoma is attached to the floor by a narrow or wide peduncle in the absence of distortion of the overlying hypothalamus. This location is most common in association with a clinical presentation of precocious puberty,[3] and surgical removal has proved curative in small case series.[26,33] Conversely, hamartomas that predominate in patients with GE directly involve and distort the hypothalamus[3,14] and have been described as being "sessile" or "intrahypothalamic." Further detailed classification into 4 types has been proposed by Fohlen et al.,[13] although a continuum of lesions likely exists.[24]

Electroencephalography Studies

Interictal EEG recordings in infants with gelastic seizures and HHs can be normal, and ictal recordings of the brief infantile seizures often are not associated with any EEG change.[6,20] Later in childhood, as seizures evolve into multiple types, a background of generalized slow spike-wave discharges without focal abnormalities suggestive of secondary generalized epilepsy may develop.[5,6] There is now strong evidence to suggest that it is the intrinsic epileptogenicity of an HH that is the origin of a gelastic seizure. This finding has been based on 1) recordings of an implanted depth electrode into a hamartoma during gelastic seizures,[23,25,29] 2) the reproduction of laughter and gelastic seizures following stimulation of an HH,[23,25] 3) the observation of ictal hyperperfusion and hypermetabolism of the hamartoma with SPECT[25] and PET imaging, and ultimately by 4) the resolution or improvement of seizures following resection, ablation, or radiation treatment of the HH.[31,32,47] Lastly, pacemaker-like activity can be found within clusters of cells in resected hamartomas, supporting the notion that epileptic properties are indeed intrinsic to the hamartomas themselves.[60]

Cognitive and Psychiatric Evaluations

Cognitive dysfunction associated with HH is considered a hallmark of the intractable GE syndrome, which can be progressive in nature and parallel the development of clinical and EEG features of secondary generalized epilepsy.[5,6] Whereas severe cognitive impairments are often present in patients with multiple seizure types and evidence of secondary epileptogenesis,[37,39] global cognitive impairments have been demonstrated prior to the onset of epilepsy in some patients, thus suggesting that the hamartoma itself may be interfering with important integrative functions essential for learning.[37] In addition, it has become clear that a spectrum of neuropsychological impairments exist,[37] and normal cognitive function may be seen in patients with milder forms of GE.[28,53]

Surgical Management of HHs

Surgical Considerations

A variety of basal surgical approaches to remove HHs have been described, including subfrontal, subtemporal, pterional, and frontotemporal.[13,34] Results of surgical interventions for HHs from 2 series in which either the pterional or frontotemporal approach was used were not promising. In those series of 1334 and 1414 patients, respectively, only 2 patients in the first and 3 patients in the second series were rendered completely seizure free. In addition, 7 patients in 1 of the series experienced serious complications,[34] including cranial nerve paresis, stroke, and even death. As a result of the modest seizure improvements coupled with a high incidence of complications, alternatives to standard basal surgical approaches have been developed to obtain a greater degree of hamartoma resection while limiting complications.

It is not clear if total or subtotal resection or partial treatment of an HH is needed to achieve seizure freedom, as reports have indicated that seizure freedom can be achieved with either strategy.[15,32] Note, however, that complete removal appears to be dependent on the size and location of the HH: the larger the lesion the less likely the chance of complete resection, and the closer the attachment to the mammillary bodies the harder and riskier complete resection will be.[45] As a result, surgical disconnection has been proposed as an alternative to removal by Fohlen et al.[13] in cases in which the tumor is large, and complete and safe resection is not possible. This strategy is believed by some to be the optimal surgical approach required to achieve a good seizure outcome with minimal risk.[13,38,45] Nonetheless, disconnection with or without resection from the mammillary bodies and the hypothalamus can be technically challenging because the plane for such a disconnection may not be well defined.

Anterior Transcallosal Interforniceal Approach

The transcallosal interforniceal approach to HHs, first described by Rosenfeld et al.[47] in 2001 and successful in 3 of 5 patients, has replaced most basal approaches to intra-HHs. Further experience has led to modifications and an evolution to the anterior transcallosal transseptal interforniceal approach to minimize forniceal retraction and reduce the risk of memory disturbances. The clinical and operative anatomy of the anterior transcallosal interforniceal approach has been described in detail[12,46,51] Hypothalamic hamartomas are typically intimately attached to one or both sides of the hypothalamus and protrude into the third ventricular cavity, making them accessible for resection or disconnection via this approach. The main advantage of this approach is the excellent surgical view provided. A second advantage is the ability to debulk and/or disconnect the HH and spare the mammillary bodies if they can be identified as well as preserve the pituitary stalk and optic chiasm. The third advantage is the avoidance of blood vessels and cranial nerves encountered in the basal approach[46] with the possibility of following the lesion into the interpeduncular fossa and prepontine cistern, if necessary. An anteriorly placed limited callosotomy is followed by careful dissection between the 2 leaves of the septum pellucidum, which allows for the interforniceal approach between the upper-

most section of the forniceal columns before they converge to form the arches of the fornix. On entering the anterior end of the roof of the third ventricle, the HH is removed using the microtip and the ultrasonic aspirator at a low setting; surgery can then proceed beyond the floor of the third ventricle into the interpeduncular cistern if necessary. When the tumor is large with significant inferior projections into the basal cisterns, a combined or staged transcallosal approach with an additional basal transsylvian approach can be used.[12]

Seizure Outcome Following the Transcallosal Approach. Enthusiasm for early results on the removal of HHs associated with GE first by the transcallosal and then by the anterior transcallosal interforniceal approach led to an increase in the use of open resection for hamartomas.[1,32,45] Results from the 2 largest series to date have demonstrated seizure freedom in 14 (54%) of 26 patients[32] in 1 series and 15 (52%) of 29 patients[45] in a second series, with a mean follow-up of 20 and 30 months, respectively. An additional 35 and 24% of patients, respectively, had a $> 90\%$ reduction in seizures. The likelihood of seizure freedom was associated with a younger age, shorter duration of epilepsy, smaller HH volume, and complete HH resection. The presence or absence of a developmental delay and the seizure type (gelastic only vs multiple seizure types) did not appear to correlate with seizure freedom. In addition to a reduction in seizure frequency after resection, significant improvements in behavior, reduced aggression, increased concentration, and improved mood have been reported. Ng and associates[32] have reported subjective improvement in behavior in 88% of patients and cognition in 58% of patients as reported by parents as early as the first few weeks following surgery. This improvement has been attributed to the decreased frequency of interictal spike-wave activity and may relate to a reversal in the epileptic encephalopathy observed in some of these patients.[15,20]

Complications of the Transcallosal Approach. Injuries to the hypothalamus on attempting complete removal of hamartomas are the most common complications reported with the transcallosal and anterior transcallosal transseptal approaches. Asymptomatic hypernatremia without polyuria was the most common endocrinological complication observed in up to 55% of patients in 1 series.[16] More overt diabetes insipidus requiring vasopressin therapy was reported in up to 15% of patients in 1 series[32] and 14% in another,[45] but it was usually transient with no need for long-term antidiuretic hormone therapy. The most commonly reported complaint after resection was difficulty with short-term memory, which occurred in almost half of all patients[21] and was persistent at 3 months in almost one-third of all patients. Weight gain or hypothalamic obesity, a known complication of surgery on the hypothalamus including tumor resections and endoscopic third ventriculostomy for hydrocephalus,[19] was seen in the early postoperative period in 45% of patients treated via the transcallosal approach. Additionally, partial or complete panhypopituitarism has been described with low thyroxine and growth hormone levels for which replacement therapy was required. Excessive sleepiness and hyperthermia have also been observed in the early postoperative period. Injury to structures beneath the hypothalamus with resection of large lesions or in combination with basal approaches can result in cranial nerve paresis[32,45] and hemiparesis[1,32] due to thalamic infarcts, although the frequency appears less than that previously seen with basal approaches.[34]

Endoscopic Resection

Transventricular endoscopic resection has been demonstrated to be a good treatment option for small intra-HHs (< 10 mm) ideally attached to only one wall of the third ventricle and exhibiting definite intraventricular extension.[13,18,30,31,38,44] The use of an endoscopic approach may be preferred over the transcallosal approach in adults in whom the septum pellucidum leaves are hard to separate, which increases the potential risk of losing the midline orientation and causing injury to the columns of the fornix. A distance of at least 6 mm from the lesion to the foramen of Monro is needed to allow safe manipulation of the endoscopic instruments within the third ventricle during removal. Removal of the hamartoma is best achieved through the foramen of Monro, which is contralateral to the hypothalamic attachment (Fig. 1). Frameless stereotactic neuronavigation is essential to accurately approach the foramen of Monro for entry into the third ventricle, particularly when the ventricle size is normal. Rigid fixation of the endoscope is essential and micromanipulation of the scope should occur after entrance into the third ventricle. The HH is usually easily distinguished from the surrounding hypothalamus as a mass projecting into the third ventricle and displaying a light brown color and a relatively avascular surface. The HH center is then debulked, and the interface with the hypothalamus is circumferentially resected. Compared with patients who underwent an open transcallosal approach, those who underwent an endoscopic resection had a clinically and statistically shorter hospital stay.[31]

Seizure Outcome Following Endoscopic Resection. The largest series of patients who have undergone endoscopic resection of their hamartomas is from the Barrow Institute, and seizure freedom was attained in 18 (49%) of 37 patients with a minimum 1-year follow-up. This outcome was similar to that seen with an open transcallosal approach at the same center in which 54% of patients were seizure free.[32] Significant improvement in behavioral disturbances after endoscopic resection has also been reported.[18,31] Assessment of outcome as measured by quality of life has been rated as very good not only in patients who are seizure free after surgery but also in those with an incomplete response to endoscopic surgical removal (Fig. 2).[18]

Surgical Complications Following Endoscopic Resection. Transient serious complications have been reported in up to 25% of patients who have undergone endoscopic resection, despite the fact that the procedure is considered minimally invasive; these complications are permanent in 7% of patients.[31] As with open surgical removal via a transcallosal approach, the most common complication after endoscopic removal was difficulty with short-term memory, occurring in 6 patients (14%) and persisting 3 months after surgery in 3 patients (7%). Details of the underlying factors causing memory disturbance were not provided; however, injury to the fornix on entry into the third ventricle following endoscopic removal as well as resection of the hamartoma from the mammillary bodies has been implicated as playing a role in memory problems.[18] Although the approach through the contralateral

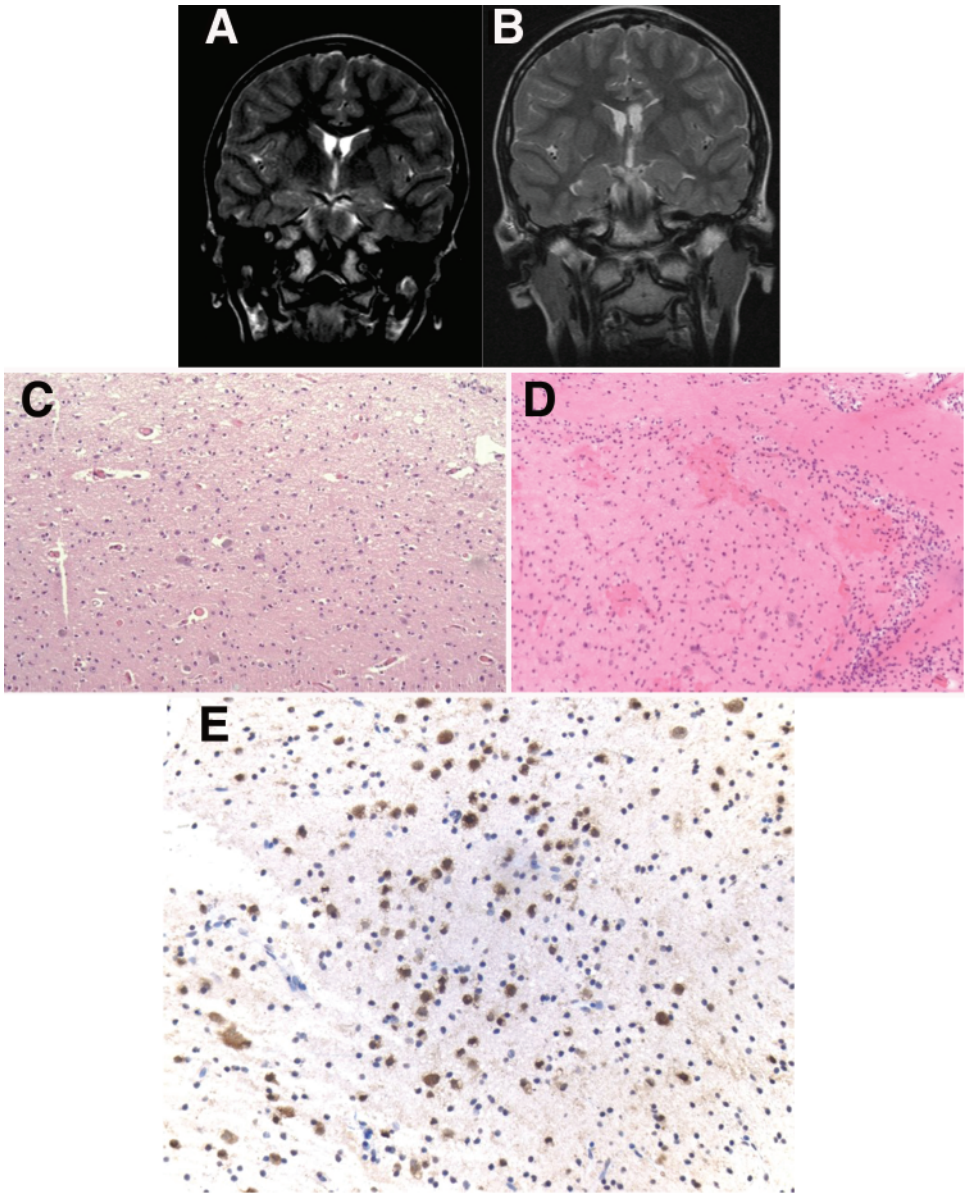

FIG. 1. Images obtained in an 11-year-old cognitively normal boy with GE and severe behavioral disturbances. The boy was seizure free after endoscopic removal of the HH. Coronal T2-weighted MR image (A) demonstrating a small right intra-HH. Postresection coronal MR image (B) revealing complete removal of the lesion. Photomicrographs showing a normal hypothalamus (C), a hamartoma with diffusely scattered nodules (D), and the presence of neurons (E). H & E (C and D), neuronal nuclear antigen (E). Original magnification × 100 (C and D), × 200 (E).

ventricle is ideal for resection of the hamartoma, a greater risk of significant memory disturbance may exist together with injury to the fornix in the language-dominant hemisphere. In a larger series,[31] hemiparesis, presumably due to thalamic perforating vessel injury, occurred in 3 patients and was believed to be related to penetration of the interpeduncular cistern at the time of the procedure. Transient weight gain > 10% of body weight was also identified in up to 10% of patients.

Radiosurgical Treatment

The safety and efficacy of radiosurgical treatment for patients with intractable epilepsy has been demonstrated in a European multicenter trial of patients with mesial temporal lobe epilepsy.[42] Long-term follow-up data have suggested that the success of radiosurgery for intractable mesial temporal lobe epilepsy is similar to that with standard microsurgical resection.[4,58] Successful lesioning of HHs by Gamma Knife surgery for the treatment of intractable GE was first described by Arita et al.[3] in 1998 and subsequently has been reported in several small case studies with Gamma Knife[27,55] and linear accelerator radiosurgical technology.[50] In the largest series,[43] among 27 patients with a minimum of 3 years of follow-up, seizure freedom was achieved in 10 patients (37%) and significant improvement

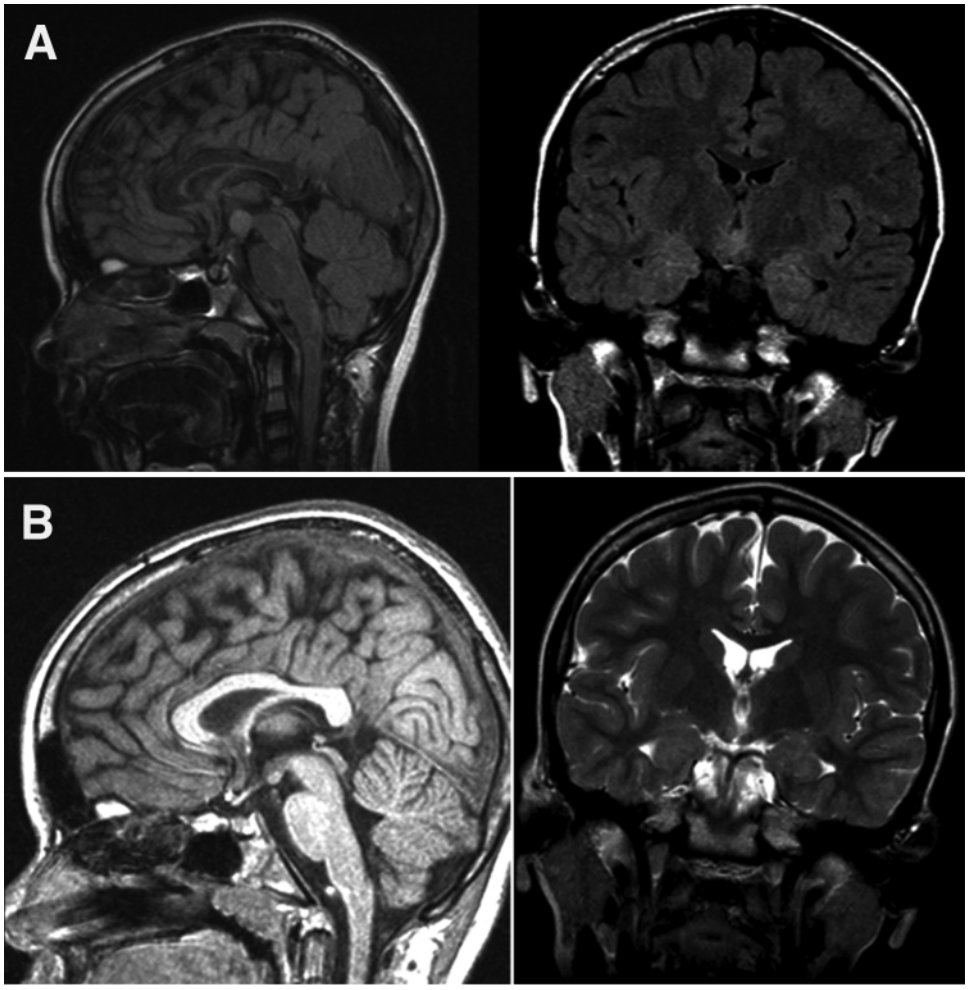

FIG. 2. Magnetic resonance images obtained in a 9-year-old boy with GE since infancy, generalized seizures, and severe cognitive and behavioral dysfunction. The patient had a > 90% improvement in seizures and behavior after endoscopic resection. Memory improved from severe dysfunction to average function. Sagittal (A) and coronal (B) FLAIR images showing an intra-HH. Postresection sagittal FLAIR (C) and coronal T2-weighted (D) MR images demonstrating residual lesion.

in seizure frequency in another 6 patients (22%). Significantly fewer gelastic seizures occurred preoperatively in the patients who became seizure free compared with those who did not. The ability to deliver optimal doses to lesion margins, particularly for small intrahypothalamic or intraventricular lesions, was also a good predictor of a positive therapeutic response. Improvements in seizures appear to follow a temporal sequence, with an early initial treatment response followed by transient worsening and a resultant reduction in and remission of seizures.[43] Similar to what occurs following open surgical procedures, patients who experienced good seizure outcome also showed behavioral and cognitive improvement. Repeated radiosurgery was possible in patients who did not respond to initial therapy, and an improved response was seen. In addition, resection is possible after radiosurgery and has been utilized to treat larger lesions. Unarguably the major advantage of radiosurgery in the treatment of HHs is its safety. Compared with other treatment options available, particularly stereotactic thermocoagulation[17,22,35] and microsurgical techniques, vascular and neurological complications, such as cognitive complications, have not been reported with the radiosurgical treatment of HH; however, only short-term follow-up data have been reported.

Interstitial Radiosurgery, or Brachytherapy

Interstitial radiosurgery, formally called "brachytherapy," involves the temporary direct or stereotactic placement of a single or multiple radioactive sources into the target volume. Energy is delivered using ^{125}I, by which high energy (up to a 200-Gy isodose) is delivered to the target with a steep falloff to the periphery, leading to central necrosis and injury to the surrounding tissue layer undergoing programmed cell death. Despite the high energy delivered, there is minimal radiation injury outside the target. The treatment is delivered over a period of 3 weeks, with a low-dose rate (1–15 cGy/hour). Such a small dose allows surrounding structures to recover from the radiation exposure and therefore minimizes the risk to surrounding vital structures including optic nerves and tracts, mammillary bodies, and brainstem.[46] In a study of 15 patients with HHs and

intractable epilepsy, an Engel Class I or II outcome was achieved in 40 and 13% of patients, respectively, with a short mean follow-up of 13.9 months. Treatment was repeated twice in 8 patients and 3 times in 1 patient. Neuropsychological assessment was not available in all patients; however, subjective improvement in attention and the ability to concentrate was reported, which was consistent with findings in other studies on the surgical treatment of HHs.[31,32,43,47] When compared with other radiosurgical procedures, interstitial radiosurgery has the advantage of a short time to produce a therapeutic effect—between 2 and 8 weeks. Compare this therapy with linear accelerator or Gamma Knife surgery, which in the short term may worsen seizures and for which a number of months are required to observe reductions in seizure frequency.[43] Although interstitial radiotherapy generally has a high safety profile, treatment complications have been reported, including implantation complications such as hematoma and infection. Specific complications of the procedure have been described and include persistent hyperphagia and transient edema at the treatment site as well as headache, fatigue, and a transient increase in seizure frequency.[46] Cognitive side effects, although reported to be minimal, reflect only a short-term follow-up in the patients reported.[40]

Stereotactic Radiofrequency Thermocoagulation

Several reports with small numbers of patients have recently demonstrated the safety and efficacy of stereotactic radiofrequency thermocoagulation for HH.[17,22,25,35] Homma and associates[22] have reported on 5 patients with HH who underwent stereotactic radiofrequency thermocoagulation for the treatment of intractable epilepsy. In all cases the hamartoma was intraventricular and < 15 mm in diameter. In 3 patients, a depth electrode was placed in the lesion by using a Leksell stereotactic system (Elekta), and recording from the hamartoma confirmed the ictal onset. After the recording, the depth electrode was replaced using the lesion electrode. Up to 74°C for 60 seconds was used as tolerated by the patients. After a mean follow-up period of 50.6 months, 3 patients were seizure free and the remaining 2 patients have $> 90\%$ improvement in seizure frequency. Transient low-grade fever developed in 3 patients, and no patient was reported to have a permanent complication related to the procedure. Additional reports have also detailed improvement in seizure frequency; however, most are limited to the description of 1 or 2 patients.[25,28,35]

Discussion

The surgical management of HHs associated with GE has been demonstrated to be an effective strategy resulting in seizure freedom in up to half of the patients with a significant remainder demonstrating an improved seizure burden. In addition, many patients have demonstrated early and sustained subjective improvements in behavior and cognitive functioning as a result of removing the hamartomas. Resective strategies, including transcallosal surgical approaches and less invasive endoscopic transventricular approaches that aim for complete lesion removal, appear to result in the greatest proportion of patients achieving seizure freedom. The main factor associated with a better seizure outcome is the completeness of the hamartoma resection. Although complete resection likely offers the highest chance of seizure freedom, such a procedure may not be necessary in all patients. Partial treatment of the lesion, as in a subtotal resection[18] or less invasive stereotactic or radiosurgical methods not intended to completely obliterate the lesion, may be similarly effective in improving seizures, behavior, and quality of life. The majority of reports to date, however, are retrospective case series at individual centers, and no randomized trials have been conducted to evaluate the best surgical treatment strategies for this rare developmental lesion.

The most common surgical approaches now include transcallosal and transventricular endoscopic approaches, and although these procedures result in better seizure control than previous basal approaches, they are not without significant risks to the hypothalamus and surrounding structures.[2,32,45,59] Memory disturbances related to forniceal retraction and the removal of hamartomas from the mammillary bodies have been demonstrated in up to one-half of patients following surgical lesion removal, and although the majority of patients and families have not reported persistent memory problems, formal evaluation was not mentioned in most cases. The impact of persistent seizures and ongoing behavioral disturbances as well as serious complications on the future quality of life in patients after hamartoma surgery is unclear. Reports on the quality of life in patients after open surgery and less invasive approaches remain restricted to small case series only. However, a high quality of life after surgery may be possible not only in patients free of seizures but also in those with persistent mild seizures and improved behavior.[18] The rate of surgical complications following less invasive stereotactic approaches, including radiosurgical lesioning and stereotactic radiofrequency ablation, appears to be lower than that reported with more aggressive resection strategies; however, in most studies detailed cognitive outcome and quality of life have not been assessed.[45]

The optimum timing of surgery for GE remains unclear; however, early intervention prior to the onset of secondary epilepsy may lead to a better seizure outcome and prevention of the behavioral and cognitive decline related to the progressive epileptic encephalopathy that may occur in some patients.[32] One of the major difficulties in determining the magnitude of improvements in cognition and behavior after surgery is that many patients demonstrate marked cognitive and developmental delays prior to intervention. As a result, the precise neuropsychological effects of surgery for HHs in these patients may be difficult to assess. Although subjective improvements in behavior and cognition are frequently reported, formal objective assessments of changes after surgery are rarely reported.[45] Documentation of improved objective cognitive performance after resection of hamartomas has rarely been provided and only once in detail.[18] One patient who had presented with a long history of GE and severe behavioral problems demonstrated severe deficits in function including visual memory, verbal memory, and executive function. Uncomplicated subtotal endoscopic resection of a 1-cm intraventricular hamartoma was performed. Postoperatively the patient had a $> 90\%$ reduction in his gelastic seizures, experienced no further generalized seizures, and demonstrated significant improvement in his behavior. Postsurgical cognitive testing revealed that visual-spatial skills and memory had

increased from severely impaired ranges to age-appropriate levels. The normalization of such severe cognitive impairments after the resection of HHs supports the notion that a reversible component of cognitive dysfunction may exist in some patients with GE and may be improved with surgical intervention.

Conclusions

The treatment of HHs associated with GE has been shown to improve seizures and behavioral disturbances with an acceptable morbidity rate by using a variety of surgical approaches. Partial treatment of HHs may be sufficient to reduce seizure frequency and to improve behavior and quality of life with limited risks. A component of reversible cognitive dysfunction may be present in some patients with HH-GE syndrome.

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