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No More Tears: Surgical Options and Outcomes in Hypothalamic Hamartomas

Long Term Outcome After Surgical Treatment for Hypothalamic Hamartoma

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Purpose: To determine long-term outcome for seizure control and clinical predictors for seizure freedom in patients undergoing surgical treatment for epilepsy associated with hypothalamic hamartoma (HH). Methods: 155 patients underwent surgical treatment for HHs and treatment-resistant epilepsy at one center (Barrow Neurological Institute at St. Joseph's Hospital and Medical Center, Phoenix, Arizona, USA) between February 2003 and June 2010. Data collection included medical record review and direct follow-up interviews to determine seizure outcome. Statistical analysis included descriptive summaries of patient characteristics and time-to-event analysis for seizure freedom. Results: Long-term survival with follow-up of at least five years since first surgical treatment was available for 108 patients (69.7% of the treatment cohort). The surgical approach for first HH intervention consisted of transventricular endoscopic resection (n = 57; 52.8%), transcallosal interforniceal resection (n = 35; 32.4%), pterional resection (n = 7; 6.5%), and gamma knife radiosurgery (n = 9; 8.3%). Multiple surgical procedures were required for 39 patients (36.1%). There were 10 known deaths from all causes in the treatment cohort (6.5%). Of these, one (0.6%) was related to immediate complications of HH surgery, three (1.9%) were attributed to Sudden Unexpected Death in Epileptic Persons (SUDEP), and one (0.6%) to complications of status epilepticus. For surviving patients with long-term follow-up, 55 (50.9%) were seizure-free for all seizure types. Univariable analysis showed that seizure-freedom was related to 1) absence of a pre-operative history for central precocious puberty ($p = 0.01$), and 2) higher percentage of HH lesion disconnection after surgery ($p = 0.047$). Kaplan-Meier survival analysis shows that long-term seizure outcome following HH surgery is comparable to short-term results. Summary: These uncontrolled observational results show that long-term seizure control following HH surgical treatment is comparable to other forms of epilepsy surgery. Late relapse (at least one year after surgery) and SUDEP do occur, but in a relatively small number of treated patients. These results inform clinical practice and serve as a comparable benchmark for newer technologies for HH surgery, such as magnetic resonance imaging-guided laser interstitial thermal therapy, where long-term outcome results are not yet available.

Epilepsy Surgery in Patients With Hypothalamic Hamartomas—Population-Based Two-Year and Long-Term Outcomes

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Objective: Hypothalamic hamartomas are benign lesions associated with drug resistant epilepsy. Surgical treatment has become an increasingly utilised approach with promising results. This study aims to evaluate seizure outcome and complications after surgery in a population-based series of patients with intractable epilepsy and hypothalamic hamartoma. Methods: All patients with hypothalamic hamartoma treated with epilepsy surgery in Sweden since 1995 with at least two years of follow-up were included. Preoperative, two-, five- and ten-year prospective longitudinal data were collected from The Swedish National Epilepsy Surgery Register. Data included seizure types and frequency, duration of epilepsy, clinical characteristics, neurological deficits, cognitive level and complications. In a subgroup from Gothenburg, we also analysed data not included in the register such as classification of hamartomas, surgical procedures and gelastic seizures. Results: Eighteen patients were operated on during the period 1995-2020. The median age at epilepsy onset was 6 months and age at surgery 13 years. Four were seizure free and another four had $\geq$75% reduction in seizure frequency at the two-year follow-up. Two of the 13 patients with a long-term follow-up (five or ten years) were seizure-free and four had $\geq$75% reduction in seizure frequency. Three had an increased seizure frequency. No major complications were seen. Five had minor complications. In the Gothenburg

subgroup all had open pterional disconnection or intraventricular endoscopic disconnection. Six of 12 were free from gelastic seizures at the two-year follow-up and six of eight at the long-term follow-up. Conclusion: This study supports surgical treatment of hypothalamic hamartomas as a safe method with a low risk of permanent complications. The seizure reduction seems to be persistent over time.

Commentary

Hypothalamic hamartomas (HHs) are congenital, nonmalignant, and nonprogressive lesions of well-differentiated cells in a disorganized matter.[1] With an estimated prevalence of approximately one case per 200 000 children,[2] they are responsible for an intriguing epilepsy syndrome that manifests with a host of different ictal semiologies including gelastic and dacrystic seizures, cognitive and behavioral impairment, and precocious puberty.[1] As such, HHs frequently necessitate surgical management, which is generally defined by their size and attachment,[3] local expertise, and available technology.[1]

Although the surgical strategies vary, HHs with a vertical attachment plane within the third ventricle (Delalande types II, III, and IV)[3] are commonly approached with transventricular endoscopic surgery (typically for lesions with generous ventricular volume and unilateral attachment) or transcallosal interforniceal approach (typically for larger lesions with bilateral attachment).[4] For HHs with a horizontal attachment plane below the floor of the third ventricle (Delalande type I),[3] pterional resection may be deployed.[4] With the advent of less invasive techniques such a stereotactic radiosurgery (SRS)[5] and thermocoagulation (radiofrequency ablation [RFA][6] or magnetic resonance imaging-guided laser interstitial thermal therapy [LITT][7]) less invasive options were added to our armamentarium. These 2 studies[4,8] provide long-term seizure outcome data on traditional surgical techniques, setting a reference point for the evaluation of newer ones that were established in the interim.

The first study[4] evaluated 155 patients who underwent surgical treatment of HHs at a single, major, epilepsy center in the United States between 2003 and 2010. More than one-third of the patients required a second intervention. The initial procedures performed were dictated by the size and attachment of the HH and consisted by transventricular endoscopic resections in most patients, followed by transcallosal interforniceal resections, and, less frequently, by pterional resections and gamma knife radiosurgery. Ten patients died, including one death related to acute postoperative complications. From the 108 surviving patients with at least 5 years of follow-up, nearly half were seizure-free regardless of the type of surgery, with univariable analysis identifying the absence of precocious puberty and the extent of lesion disconnection as the most important predictors of success. Most remaining patients demonstrated substantial seizure frequency reduction.[4]

The second study[8] evaluated 18 patients who underwent surgical treatment for HHs at multiple centers in Sweden from 1995 to 2020. Most were treated with either intraventricular endoscopic or open pterional disconnections. No major complications were noted. At the 2-year follow-up, the median seizure frequency reduction for the whole cohort was 71% with 4 patients being free of seizures. Fairly similar responder and median seizure frequency reduction rates were noted in the 10 patients with longer follow-up.[8] These rates appeared lower compared to prior endoscopic disconnection series where epilepsy duration was shorter, indirectly identifying disease duration as a predictive factor and highlighting the value of earlier intervention.[9] Postoperative cognitive testing was only available in half of the cohort at the 2-year follow-up time with optimal trends reported in a single patient.[8] Although the median anti-seizure medications (ASMs) burden remained unchanged, some of the seizure free patients successfully discontinued their ASMs in the long run.[8]

Both studies[4,8] provide valuable insight into long-term seizure outcomes and complication rates of traditional surgical approaches against HHs across the Atlantic. They also identify potential predictors of seizure freedom. Yet, they are both fraught by referral and selection biases, local practice habits influenced also by the timeline for innovation in the available surgical options and patients' loss in follow-up. Most importantly, they both fall short in evaluating cognitive, behavioral, quality of life, and endocrinological outcomes.

These limitations notwithstanding, these studies[4,8] deliver the message of successful and relatively safe surgical treatment of HHs in the long run, comparable with other epilepsy syndromes, irrespective of the type of HH and the deployed surgical approach. They also act as useful benchmarks of traditional surgical procedures for evaluation of novel techniques that emerged in the past decades.

Several questions about this fascinating epileptogenic substrate remain, at least partially, elusive. For example, while we realize that HHs constitute a model of epileptic encephalopathy and that genetic factors like germline mutations in GLI3 may play a role in the development of the epileptic network,[10] we still do not fully understand their molecular, histopathological, and electrophysiological underpinnings. Similarly, although we appreciate that certain types of HHs like the parahypothalamic ones are linked to endocrinopathy without the additional comorbidities,[1] we lack adequate in vitro and in vivo modeling paradigms to account for the observed variability in epileptic, neuropsychiatric, and endocrinological manifestations among individuals. Foremost, despite the intuitive prevailing concept that minimally invasive approaches portend to less surgical morbidity,[1] we have no head-to-head comparisons to evaluate open versus minimally invasive procedures, those that are functionally-based versus image-guided, and those that aim in resection versus disconnection of the lesion. Although

meta-analytic evidence suggests that LITT is superior in seizure freedom over RFA and SRS, and that RFA is related to lower but statistically nonsignificant complication rate,[11] confirmation with direct comparative studies, standardized management guidelines, and assessment of novel techniques such as focused ultrasound, neurostimulation, and optogenetics are required. Lastly, preliminary evidence suggests that successful treatment of HHs results in postoperative gains in intellectual functioning,[6,12] highlighting the need for a more holistic, multicenter evaluation of the surgical management of this epilepsy syndrome that incorporates markers of cognitive, behavioral, and hormonal function, in addition to the traditional focus on seizure outcomes.

Overall, HHs are indeed no laughing matter.[13] Yet, the epimythium of these studies is that they are by and large treatable over the long haul. And with the addition of minimally invasive techniques in our arsenal, there is tangible hope for a brighter future. No more tears!

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