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Original Article

Surgical Treatment of Hypothalamic Hamartoma Causing Refractory Epilepsy: A Systematic Review

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ABSTRACT: ***Background:*** Hypothalamic hamartomas (HHs) are a known cause of refractory focal epilepsy. Advancement in microsurgical techniques and introduction of stereotactic ablative methods have led to improved complication rates, but the effect on seizure control is still to be determined. In this systematic review, we present a thorough analysis of published literature on the outcomes of various surgical treatments of HHs for refractory epilepsy. ***Methods:*** A literature search using the MedLine, SCOPUS and Cochrane databases was conducted. All English language studies describing surgical treatment of HH with refractory epilepsy, with a minimum of three patients and a follow-up of at least one year, were identified. ***Results:*** An initial selection of 55 studies was reduced to 41 after combining studies from the same groups; 14 open, 4 endoscopic, 8 Gamma Knife radiosurgery (GKRS), 9 laser interstitial thermal therapy (LITT) and 6 radiofrequency thermocoagulation (RF-TC) studies were included. From a total of 832 patients, 209 underwent open (25.1%), 80 endoscopic (9.6%), 124 GKRS (14.9%), 229 LITT (27.5%) and 190 RF-TC (22.8%). Engel I or ILAE 1 or 2 was achieved in: open 115 (55.0%), endoscopic 38 (47.5%), GKRS 49 (39.5%), LITT 176 (76.9%) and RF-TC 128 (67.4%). Invasive surgeries (open and endoscopic) had a higher incidence of neurological complications (27.0%) than ablative surgeries (GKRS, LITT, RF-TC) (7.2%). Reoperation rates were higher for ablative surgeries (23.8%) than invasive surgeries (9.0%). ***Conclusion:*** Surgical treatment of HH causing refractory epilepsy is effective. RF-TC and LITT surgery types have the highest Engel class I outcomes, and ablative surgeries have a lower neurological complication profile compared to open and endoscopic approaches.

RÉSUMÉ : Traitement chirurgical des hamartomes hypothalamiques à l'origine d'une épilepsie réfractaire : une revue systématique
Contexte : Les hamartomes hypothalamiques (HH) sont une cause connue d'épilepsie focale réfractaire. Les progrès des techniques microchirurgicales et l'introduction des méthodes ablatives stéréotaxiques ont permis d'améliorer les taux de complications, mais leur effet sur le contrôle des crises reste à déterminer. Dans cette revue systématique, nous entendons présenter une analyse approfondie de la littérature publiée au sujet des résultats des divers traitements chirurgicaux des HH en lien avec l'épilepsie réfractaire. ***Méthodes :*** Une recherche documentaire a été effectuée à l'aide des bases de données Medline, SCOPUS et Cochrane. Toutes les études en anglais décrivant le traitement chirurgical des HH en lien avec l'épilepsie réfractaire, portant sur au moins trois patients et avec un suivi d'au moins un an, ont été identifiées. ***Résultats :*** Une sélection initiale de 55 études a été réduite à 41 après avoir regroupé les études provenant des mêmes groupes. Au total, 14 études portant sur des interventions ouvertes, 4 études portant sur les traitements endoscopiques, 8 études portant sur la radiochirurgie par scalpel gamma (« GKRS »), 9 études portant sur la thalamotomie par laser (« LITT ») et 6 études portant sur la thermocoagulation par radiofréquence (« RF-TC ») ont été incluses. Sur un total de 832 patients, 209 ont subi une chirurgie ouverte (25,1 %), 80 une chirurgie endoscopique (9,6 %), 124 une chirurgie de type « GKRS » (14,9 %), 229 une chirurgie de type « LITT » (27,5 %) et 190 une chirurgie de type « RF-TC » (22,8 %). L'échelle de résultats Engel I ou la classification (niveaux 1 et 2) de la International League Against Epilepsy (ILAE) ont été atteintes dans les proportions suivantes : chirurgie ouverte : 115 patients ou 55,0 %, chirurgie endoscopique : 38 patients ou 47,5 %, « GKRS » : 49 patients ou 39,5 %, « LITT » : 176 patients ou 76,9 % et « RF-TC » : 128 patients ou 67,4 %. Les chirurgies invasives (ouvertes et endoscopiques) ont présenté une incidence plus élevée de complications neurologiques (27,0 %) que les chirurgies ablatives (« GKRS », « LITT », « RF-TC » : 7,2 %). À noter aussi que les taux de réintervention ont été plus élevés pour les chirurgies ablatives (23,8 %) que pour les chirurgies invasives (9,0 %). ***Conclusion :*** Le traitement chirurgical des HH à l'origine d'une épilepsie réfractaire est efficace. Les interventions chirurgicales de type « RF-TC » et « LITT » ont donné à voir les meilleurs résultats selon l'échelle de résultats d'Engel I tandis que les chirurgies ablatives ont présenté un profil de complications neurologiques plus faible que les interventions ouvertes et endoscopiques.

Keywords: Endoscopic surgery; gamma knife radiosurgery; hypothalamic hamartoma; laser ablation; laser interstitial thermal therapy; open resection; radiofrequency thermocoagulation; refractory epilepsy

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Highlights

- LITT and RF-TC outperformed open and endoscopic surgeries in seizure freedom. Ablative methods showed higher reoperation rates vs. open/endoscopic.
- Open/endoscopic surgeries had higher neurological and vascular risks, and ablative techniques posed significant endocrinological complications.
- Minimally invasive ablative techniques are preferred for refractory epilepsy, but open surgery remains critical for large HHs.

Introduction

Hypothalamic hamartomas (HHs) are aberrant congenital lesions arising from the ventral hypothalamus and present in 1 out of 200,000 children.[1] Patients with HHs can present in early childhood with precocious puberty, intellectual disability, aggressive behavior and epilepsy.[2] There are two main types of HHs: pedunculated (greater association with precocious puberty) and sessile (greater association with epilepsy).[3] The most common seizures associated with HHs, gelastic (laughing) seizures, are usually resistant to anti-epileptic drugs and often require surgery for definitive treatment. In addition to gelastic seizures, these patients often develop focal seizures with impaired awareness, dacrystic (crying) seizures, absence seizures, generalized tonic-clonic seizures and even infantile spasms. These accompanying seizures represent a wider seizure network and are harder to control compared to gelastic seizures alone.

Prior to the 1990s, there was hesitation to surgically manage HHs because of fear of hypothalamic damage and severe complications along with an uncertainty that the epileptogenic focus truly lies within the hamartoma.[4] Eventually, various open and endoscopic approaches were developed to resect or disconnect the lesion, including transcallosal anterior interforniceal approach, pterional or orbitozygomatic approach, transtemporal) and the endoscopic transventricular approach.[2,5] The efficacy of any of these approaches depends on the size of the lesion and its extension. Per Delalande et al., these lesions can be classified into four types (I–IV) based on location and extension of the lesion.[6] Several nearby neurovascular structures such as the optic chiasm, oculomotor nerve, pituitary stalk, perforating vessels off the internal carotid artery and the hypothalamus itself must be preserved to prevent neurological, vascular and endocrinological complications that can occur after surgery. The desire for safer, less invasive procedures for these difficult lesions has led to the use of Gamma Knife radiosurgery (GKRS), laser interstitial thermal therapy (LITT) and radiofrequency thermocoagulation (RF-TC).

The goal of this paper is to compile and summarize results from several studies examining these various procedures to evaluate their efficacy and risk profile.

Materials and methods

Data sources

The PICO process was used to frame the question for our systematic review – **P**atient/problem: patients with HH causing seizures/epilepsy; **I**ntervention: surgical treatment; **C**omparison: between surgical treatments; **O**utcomes: response to treatment measured by seizure freedom and seizure reduction. Secondary outcomes included neurological deficits, cognitive deficits, endocrinological deficits and postoperative complications.

We performed a comprehensive literature search of MEDLINE and Embase. References from published articles were also evaluated. English language articles published from 1980 onward in peer-reviewed journals, with a minimum of three patients and at least one year of follow-up after surgery, were included. Both adult and pediatric populations were included. Case reports were excluded. The PRISMA protocol is outlined in Figure 1.

The following keywords and number of studies found were *Hypothalamic Hamartoma* (714), *Hypothalamic hamartoma with epilepsy* (405), *Surgical treatment for hypothalamic hamartoma* (265), *Surgical treatment for hypothalamic hamartoma with epilepsy* (208), *Open surgery for hypothalamic hamartoma* (35), *Endoscopic surgery for hypothalamic hamartoma* (62), *Radiofrequency thermocoagulation for hypothalamic hamartoma* (21) and *Laser ablation for hypothalamic hamartoma* (35). Studies were further divided into those that described multiple surgical methods and then those that described purely open resection, laser, endoscopy, GKRS, Vagus Nerve Stimulator (VNS), callosotomy and RF-TC. Pooled analysis of patients in each subgroup was performed. Outcomes and complications with each approach were analyzed. Multiple studies from the same group with the same patient population were evaluated separately, and only the latest study was included to ensure there was no repetition of patients. Studies were selected by one author, FAM, and further reviewed by AS and AB.

The data was extracted using pre-planned tables. The following variables were considered: *demographics and seizure details*: gender, age at seizure onset, presurgical duration of epilepsy, type of seizures (seizure semiology was classified on the basis of the definitions proposed by the ILAE classification), frequency of seizures, intellectual disability (assessed with formal neuropsychological testing or level of schooling); *presurgical work up*: results from interictal electroencephalogram (EEG), ictal EEG, preoperative invasive monitoring, Magnetoencephalography, CT or MRI, ictal Single Photon Emission Computed Tomography, Positron Emission Tomography studies; *surgery*: age at surgery, type of surgery (resective[e.g., open, endoscopic, disconnection, combined], ablative [LITT, RF-TC, GKRS] and modulatory [DBS, VNS]). Histopathological findings, postoperative complications and duration of follow-up were included. Seizure outcome was classified with the Engel classification or ILAE classification as described by the authors, and the following scheme was used to equate results: Engel 1: seizure free = ILAE 1 or 2; Engel 2: rare disabling seizures = ILAE 3 = reduction by $> 90\%$; Engel 3: worthwhile improvement = ILAE 4 = reduction by $> 50\%$; Engel 4: no worthwhile improvement = ILAE 5/6 = not improved by $> 50\%$. The primary outcome was seizure freedom as defined by the authors in each study, that is, seizure-free status for at least ne year at the last reported follow-up.

Data collection and analysis

Statistical Package for Social Sciences (V.24 SPSS IBM, Armonk, NY) was utilized to record and analyze data. Continuous variables were reported using means, medians, standard deviations and ranges. Categorical variables were reported using frequencies and percentages. Risk ratio and confidence intervals (CI) were calculated. For continuous variables (e.g., age at seizure onset, duration of epilepsy and age at surgery), mean differences with corresponding 95% CI, between patients with seizure freedom and patients with recurrent seizures, were calculated. We considered associations statistically significant for p values < 0.05.

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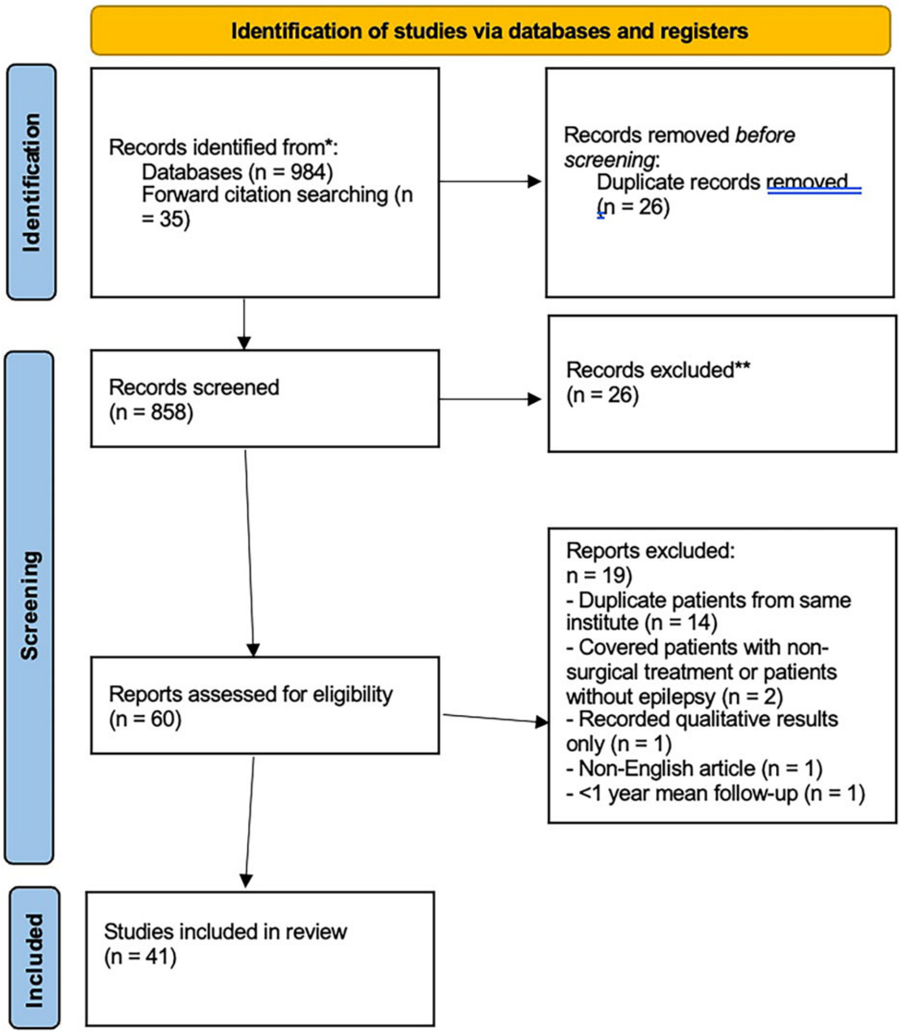

Figure 1. Study selection flow chart.

Results

Demographics

In the studies selected for analysis, there were 832 patients with an average age of 13 years (467 males, 240 females). For patients who received open and endoscopic surgeries, the average age was 12.5 and 14.9 years, respectively, with a male-to-female ratio of 74:24 and 44:36, respectively. The average age for those who received GKRS, LITT and RF-TC surgeries was 20.7, 10.1 and 11.3 years, respectively, with male-to-female ratios of 79:45, 157:65 and 113:70, respectively.[2,7–13] Some studies did not include the age and/or gender breakdown of the patients in their studies, and so those studies were excluded from for average age and gender analysis.[8,14–23]

Among the studies that included the HH classification, 16.9% of the patients in open and endoscopic patients had large or giant HHs (Delalande IV, Régis 4–6 or Valdueza IIb), equaling the 16.9% for patients in studies covering the three ablative surgeries.[4,6,19]

Regarding seizure type, at least 86% of patients from each surgical type experienced gelastic seizures. Lastly, among studies that reported previous operations, 141 patients had previous operations, with 91.5% of them reporting for ablative surgeries.[24–26]

Outcomes

Open surgeries led to seizure freedom (Engel I or ILAE 1 or 2) in 55.0% of the time compared to 47.5% for endoscopic surgeries.[17,18,27,28] The seizure freedom rate was 39.5% for GKRS, 76.9% for LITT and 67.4% for RF-TC.[11,19,22,23,27,29–33] The total seizure freedom rate for open and endoscopic surgeries was 52.9% compared to 72.6% for the three ablative surgery types combined. The reoperation rate for open and endoscopic surgery patients was 9% compared to 23.8% for ablative surgery patients.[34] The summary of outcomes for these surgeries is outlined in Table 1.

Complications

The complications experienced by patients after surgery were divided into neurological (hemiplegia, short-term memory loss, disturbance of consciousness, Horner's syndrome, weakness, oculomotor nerve palsy, ataxia, aphasia, mutism, etc.) vascular (bleeding, ischemia), infection, weight gain and endocrinological (cortisol and thyroid abnormalities, hyperphagia, poikilothermia, electrolyte abnormalities, etc.) and were recorded as number of instances as opposed to number of patients (meaning multiple complications could have been experienced by one person).

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Table 1. Summary of outcomes for the surgical treatment options for hypothalamic hamartomas

Surgical treatment type	Mean age (yrs); M:F ratio	Seizure freedom rate (Engel I or ILAE 1 or 2) %	Neurological complication instance rate %	Most common neurological complications	Endocrinological complication instance rate	Most common endocrinological complications	Number of Studies Pre-2010	Number of Studies Post-2010
Open	12.5; 74:24	55	26.8	Short-term memory impairment, CN III palsy, transient hemiparesis	29.2	SIADH, DI, thyroid dysfunction	6	8
Endoscopic	14.9; 44:36	47.5	27.5	Short-term memory impairment, CN III deficit	5.0	Transient DI	2	2
GKRS	20.7; 79:45	39.5	5.6	Episodic memory loss	4.0	Transient poikilothermia	3	4
LITT	10.1; 157:65	76.9	8.7	Short-term memory deficit, Horner's syndrome	45.2	Thyroid dysfunction, hypocortisolism	0	9
RF-TC	11.3; 113:70	67.4	6.3	Memory disturbance, transient CN III palsy	78.4	Transient hyponatremia, hypopituitarism	1	5

GKRS = gamma knife radiosurgery; LITT = laser interstitial thermal therapy; RF-TC = radiofrequency thermocoagulation; ILAE = International League Against Epilepsy; CN III = cranial nerve III; SIADH = syndrome of inappropriate antidiuretic hormone secretion; DI = diabetes insipidus.

Among patients with open surgeries, there were 56 instances of neurological complications out of 209 (26.8%).[6,14,25,30,35–41] For endoscopic surgeries, the neurological complication rate was 27.5%. The neurological complication rates for GKRS, LITT and RF-TC were 5.6%, 8.7% and 6.3%, respectively. The total neurological complication incidence rate for open and endoscopic surgeries was 27.0% compared to 7.2% for the ablative techniques.

Among the 543 patients who received ablative surgeries, there was only 1 instance of a vascular complication compared to 19 in the open and endoscopic surgeries. The two surgery types with the highest incidence of postop weight gain were open (11.0%) and RF-TC (27.9%). The endocrinological complication incidence rate for open and endoscopic surgeries was 22.5% compared to 38.7% for ablative surgeries. The majority of the endocrinological complications from ablative surgeries come from RF-TC with a 77.9% rate. The follow-ups for the patients in this systematic review ranged from 1 to 15 years. Detailed data for all types of surgical interventions can be found in supplemental tables 1–12.

Quality assessment

The quality of each study was evaluated with the Newcastle-Ottawa Scale and can be found in the supplementary document table 11.

Discussion

Demographics

There was nearly a 2:1 male-to-female ratio among the patients in our systematic review. While it is unclear as to why the discrepancy between males and females was so large, there is a male predominance among patients with epilepsy secondary to HHs. In fact, according to Zuniga et al., males are at higher risk for HH-induced epilepsy with a ratio of 1.3:1.[42] It remains unclear as to why this condition is more predominant in males than females. Patients among each surgical type suffered from gelastic seizures, and there was an equal percentage of large HHs among patients in the various surgical types. These similarities among these groups allow for a more direct comparison in outcomes.

Outcomes

There are various surgical treatment modalities that have been shown to effectively lower the seizure burden caused by HHs. The goal of this paper was to collect several studies for the various surgical treatments for HH refractory epilepsy to determine which operations yield the best results. One key outcome measure is the percentage of patients who achieve seizure freedom (Engel I or ILAE 1 or 2). LITT and RF-TC surgeries yielded the highest rates of seizure freedom, followed by open, endoscopic and lastly GKRS.[4,15,21,32,38,39,43,44] However, ablative surgeries yielded a much higher reoperation rate than open and endoscopic surgeries. One possible explanation is that these ablative surgeries can safely be repeated if the first surgery does not help the patient reach seizure freedom. It is important to note that while more patients benefit from ablative surgeries, that does not necessarily mean that open and endoscopic techniques should be abandoned for these patients. The key to achieving seizure freedom is to either resect this inherently epileptogenic lesion or completely disconnect the epileptogenic networks that travel from the HH to the rest of the brain. Certain open approaches may give the surgeon a better chance of achieving this compared to other types of surgery. For example, the transcallosal interforniceal approach may be preferred for large HHs with a significant intraventricular component superior to the optic tracts.[45] In addition, in areas with minimal resources or limited training in new technologies, open procedures would still be appropriate for various HHs. Endoscopic procedures may be preferred for the treatment of small type II HH lesions and part of the staged treatment for small type III HH lesions, where ventricular morphology is favorable. While GKRS had the lowest seizure freedom rate and is known for its delayed efficacy,[19] it is a safe, noninvasive procedure that can be repeated more easily than open surgeries. Finally, while stereotactic radiofrequency ablation techniques offered the highest seizure freedom rate, there were very few patients with giant HHs in our review. Therefore, more studies need to be completed to determine the efficacy of ablative techniques on larger HHs. Type IV HHs can pose a significant challenge, where surgical disconnection may be superior to ablative techniques.

Complications

In addition to seizure freedom and reoperation rates, we need to analyze instances of various types of complications experienced by patients to learn about the risks of the various procedures. Open and endoscopic surgeries resulted in significantly more neurological complications than ablative surgeries. This is likely part of the reason why GKRS, LITT and RF-TC have become more widely used in the treatment of HHs. The use of various imaging modalities such as fMRIs to identify the specific part of the HH responsible for seizures has allowed for more precise targeting for ablative procedures. However, endocrinological complications were more prominent in our RF-TC patients than in patients for every other surgical type. The majority of the endocrinological complications from ablative surgeries come from RF-TC with a 77.9% rate. The risk is lower with LiTT, perhaps due to the added protection to the surrounding structure by the cooling-off mechanism achieved via the irrigation channel around the laser catheter. This indicates that while we expect ablative procedures to yield fewer complications than resection or disconnection surgery, each of these surgeries can result in several types of complications.

Seizure 'freedom'

Seizure freedom in HHs is the goal, but this is often an ambiguous endpoint as some studies depicting high seizure freedom rates are referring to improvement in gelastic seizures. The secondary focal seizures that occur in these patients are not always accounted for in the analysis, and hence, a false sense of high seizure freedom rates is perceived. For example, Curry et al. cited that 93% of the patients in the study were free from gelastic seizures one year after laser ablation with little information on the presence of secondary seizures.[23]

Limitations

There are some limitations in our systematic review. Data present in the studies is heterogeneous, and variable selection differs due to variation in reporting methods. Some studies summarized outcomes for their population of patients but did not report the outcomes for each individual patient. As a result, our analysis of the data was limited. In future studies, it would be helpful for patient data to be reported in a standardized format. This strategy could facilitate the comparison of outcomes among patients who have this uncommon entity.

Conclusion

In summary, the minimally invasive ablative techniques, LITT and RF-TC, led to the highest rates of reduction of gelastic seizures. Given this and the fact that these techniques can be safely repeated, these should be strongly considered for any patient with refractory epilepsy secondary to HHs. However, there is still a role for open surgical methods particularly for large type III and type IV lesions. This is particularly important in areas where ablative technologies may not be available.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2025.10385.

Author contributions. NH: Data collection, literature review, manuscript writing

AS: Data collection, literature review, manuscript writing

MUK: Literature review, manuscript writing, editorial process, approval of the final manuscript

AB: Data collection, literature review, manuscript writing

MST: Expert commentary, manuscript writing, editorial process, approval of the final manuscript

FAM: Conceptualization, expert commentary, manuscript writing, editorial process, approval of the final manuscript

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