

Review Article

Hypothalamic Hamartomas: A Review

José Armando Díaz-Martínez^{1*}, José Ascención Arenas-Ruiz²,
Abril Antonia Quezada-Bautista¹, José Fernando Rodríguez-
Ascuntar¹, Guillermo Axayacalt Gutiérrez-Aceves¹, and Sergio
Moreno-Jiménez¹

¹Department of Neurosurgery, National Institute of Neurology and Neurosurgery, México

²Department of Pediatric Neurosurgery, Hospital Infantil de México, México

Abstract

Epilepsy is the most frequent manifestation of hypothalamic hamartomas, being in most cases drug-resistant, which lead to difficulties in the management of these patients, requiring in many cases surgery for its control. The occurrence of psychiatric co morbidity and cognitive impairment is frequent. Nowadays the increasing evidence of hypothalamic hamartomas can be treated effectively with a variety of neurosurgical approaches. Selection of treatment modalities depends on type and size of the HH and the surgeon's experience. We discussed the clinical features, pathology, diagnostic studies, neurosurgical techniques with the advantages and disadvantages of the different treatment modalities.

ABBREVIATIONS

HH: Hypothalamic Hamartoma; CPP: Central Precocious Puberty; GS: Gelastic Seizures; GnRH: Gonadotropin - Releasing Hormone; IQ: Intelligence Quotient; EEG: Electroencephalogram; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; FDG-PET: Fluorodeoxyglucose - Positron Emission Tomography; SPECT: Single Photon Emission Computed Tomography; SRS: Stereotactic Radiosurgery; GKS: Gamma Knife Surgery; SRT: Stereotactic Radiofrequency Thermocoagulation; SLA: Stereotactic Laser Ablation

INTRODUCTION

Hypothalamic Hamartomas (HH) are a rare developmental benign heterotopic non- neoplastic lesion, located in the region of the hypothalamus, arising from the tuber cinereum and floor of the 3rd ventricle. The incidence is unknown, but depending on the series it has been estimated to be from 1 in 50,000 - 100,000 [1] to 1 in 1,000,000 [2]. There is a moderate male predominance. HH are usually sporadic caused by an anomaly of neuronal migration that probably occurs between gestational days 33 and 41. Occasionally it may be associated with the Pallister-Hall syndrome, an autosomal dominant syndrome caused by GLI3 frame shift mutations on chromosome 7p13, with anomalies including HH, pituitary abnormalities such as aplasia or dysplasia, hypopituitarism, from an asymptomatic bifid epiglottis to a severe form with laryngotracheal cleft, imperforate anus, renal abnormalities and polydactyly [3]. HH are characterized by intractable seizures, Central Precocious Puberty (CPP),

*Corresponding author

Jose Armando Diaz Martinez, Department of Neurosurgery, National Institute of Neurology and Neurosurgery, Radioneurosurgery Unit, Av. Insurgentes Sur No. 3877, Col. La Fama, México City, México, Zip Code: 14269, Tel: 5255-5606-3822; 4472; Email: jose.diazmn@uanl.edu.mx

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Keywords

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cognitive impairment, emotional and behavioral disturbances [4,5]. One of the main features of hamartoma is its intrinsic epileptogenic activity, due to the presence of small nodules of GABAergic interneurons with spontaneous electrical activity [6]. The prevalence of epilepsy associated with HH is estimated to be 1 in 200,000 [7]. Gelastic Seizures (GS) are the hallmark feature commonly present in early childhood, but patients may also develop other types of seizure. Epilepsy associated with HH is characteristically refractory to treatment with antiepileptic drugs, being exceptional the achievement of good seizures control despite the administration of high doses of these drugs. The major endocrine abnormality is the CPP, which tends to occur considerably earlier than idiopathic CPP [3], which has been reported to respond to long-acting Gonadotropin- Releasing Hormone (GnRH) analogue therapy that down-regulate GnRH receptors [8]. Several microsurgical or endoscopic approaches have been used, all with significant surgical risk. For this reason, in recent years, new techniques have been developed including radiosurgery and radio thermal ablation with acceptable results for crisis management and cognitive and behavioral improvement [9,10]. In the present review, we discuss the diagnostic, clinical and pathological characteristics, and the different modalities of management of the HH.

Clinical aspects

The association among HH, GS and CPP has caused great interest since the time when Breningstall described the characteristics of this pathology [11,12]. Disease severity is

highly variable, ranging from asymptomatic or oligosymptomatic presentations to catastrophic neurological presentations [13-15].

Seizure characterization

The intimate relationship with the mammillary bodies, fornix and mammillothalamic tracts plays an important role in the epileptogenesis associated with HH [16]. In general, epilepsy in these patients are pharmacoresistant and ends as a severe epileptic encephalopathy and catastrophic epilepsy of childhood [17-19]. GS are the most characteristic and frequent manifestations in patients with HH, whilst it is not pathognomonic. GS usually beginning in childhood, they have been described even in the newborn period, and are manifested by stereotyped and frequent episodes, sometimes in clusters, of grimacing or inappropriate laughter, without feeling of joy, and usually accompanied by autonomic signs such as tachycardia, altered breathing, facial redness, pupil dilation and sweating. Autonomic manifestations may occur by changes in the limbic system, the adrenergic system and the hypothalamic-pituitary axis [20]. In patients without neurosurgical intervention it may be a progression to other seizure types such as focal seizures, evolving to a bilateral convulsive or generalized seizures [21-23]. Its development is attributed to a process of secondary epileptogenesis [17].

Central precocious puberty

CPP is considered relatively common in children with HH, and can be defined as the appearance of secondary sexual characteristics before the age of eight in females and before the age of nine in males. This endocrine disorder is a finding that is described in several patient series with HH and GS with a frequency of 30-40% [24-26]. Most of the patients (86.4%) with isolated CPP revealed a HH without touching the 3rd ventricle [27,28,4]. Half of them were pedunculated and 40.9% of the masses showed a diameter less than 10 mm [27]. Furthermore, most of HH with CPP contacted the infundibulum or tuber cinereum and were larger than those not associated with CPP [29]. The pathophysiology is not fully elucidated. Immunohistochemistry studies revealed the presence of GnRH-variant neurons in some HH with CPP [30]. Another hypothesis proposes that these neurons function as a heterotopic GnRH pulse-generator. However, in other cases related to CPP, GnRH immunoreactivity was absent. Pathological examination showed that HH was usually composed of an intermixed array of neurons, glia, and myelinated fibers [31]. This research implies that some HH induce sexual precocity by activating endogenous GnRH secretion via glia-derived factors. Otherwise, HH is not usually associated with other endocrine alterations as growth deficit, diabetes insipidus, hypogonadism, etc., in contrast to other hypothalamic pathologies such as astrocytomas, gliomas or craniopharyngiomas, in which its incidence is high.

Cognitive impairment and behavior disorder

Cognitive impairment and behavior disorders are common findings in patients with HH and seizures [32-34]. They have been correlated with the frequency and severity of the seizures, but there is a debate at this point since some series have shown that cognitive deficits already exist before the onset of crises [35].

Cognitive impairment

Frattali et al., reported a series of eight patients with medically refractory epilepsy having mild to severe cognitive deficits [33]. The severity of the cognitive impairment was correlated to the severity and frequency of the GS and focal seizures. In another series, patients with HH involving cortical association areas and the amygdala and hippocampus formation displayed cognitive impairment to a vary extent [36,37]. Almost half of the subjects had severe global memory deficits [38]. Another report described some patients of HH with cognitive impairment which includes 83.3% oppositional defiant disorder and 75% attention-deficit hyperactivity disorder [1]. The evaluation on cognitive abilities in patients with HH and GS report not only results on global Intelligence Quotient (IQ) performance but also other cognitive processes like attention or material-specific memory functions [35].

Behavior disturbances

Significant rates of attention deficit hyperactivity disorder, aggression, anxiety, and defiant disorder were noted in HH. Weissenberger et al., demonstrated oppositional defiant disorders and attention hyperactivity disorders in the majority of the patients [1]. The final proof of a direct functional role of epilepsy in cognitive and behavioral changes can only be shown with certainty when there is a marked improvement in these fields with successful surgical therapy of epilepsy. Surgical resection is safe with a favorable outcome of epilepsy in 50% with significant improvement in behavior and marginal change in cognitive functions [39,40]. At this point in time, however, there are insufficient data to enable the prediction of which patients will undergo a clinically severe course or the better time to suggest surgical treatment.

Diagnosis and medical approach

Electroencephalogram: Several studies have clearly demonstrated the intrinsic epileptic character of HH based from direct recordings from the HH itself. Ictal discharges during GS were confined to the hamartoma, and direct stimulation of the inserted depth electrodes generated GS. The excellent outcome of cases where surgical resection was possible also supports this fact. The surface Electroencephalogram (EEG) has limitations to demonstrate epileptiform activity in this pathology, due to the deep location of this lesion and the complex hamartoma connections [41]. In the early stages of the disease, interictal EEG is usually normal and GS crises show diffuse depression of baseline activity [42,43]. New studies indicate that GS originates in the HH, and propagates through the left fornix of the temporal lobe, and later through the cingulate fasciculus to the left frontal lobe [44].

Neuroimaging: On conventional axial CT images, the diagnosis can be challenging, depending on slice position and thickness, although with more recent volumetric scans with coronal and sagittal reformats, the abnormality is easier to identify. Non-enhanced CT scan reveals a homogeneous nodule with obliteration of the suprasellar cistern and anterior 3rd ventricle, iso or hypodense compared with the grey matter. HH do not enhance on high- dose contrast-enhanced CT [45]. The MRI

is the method of choice in suspected cases, pedunculated HH are shaped like a collar button on sagittal T1WI, extending inferiorly into the suprasellar cistern. Signal intensity is usually isointense to normal gray matter on T1WI and iso- to slightly hyperintense on T2/FLAIR (Figure 1). The degree of T2 hyperintensity is directly related to the proportion of glial versus neuronal tissue in the lesion. HH do not enhance following contrast administration [45,46]. The MRI spectroscopy shows mildly decreased N-acetylaspartate and slightly increased choline, consistent with reduced neuronal density and relative gliosis. Myoinositol is elevated, which is consistent with increased glial component compared to normal brain [47,48]. Ictal FDG-PET scans in HH with GS are rare. Palmini et al., reported one patient who demonstrated ictal hypermetabolism localized to the region of the HH during gelastic status [23,49]. Ictal SPECT studies have clearly demonstrated HH hyperperfusion. In the three patients of Kuzniecky et al., there was in addition absent activation of the cortex but coactivation of the thalamus consistent with seizure propagation to the anterior nucleus of the thalamus via the mamillothalamic tract [50,51,49].

PATHOLOGY

Hamartoma is a term used to describe a disorganized mass of otherwise normal cellular elements that rarely invades surrounding structures, in this case, the hypothalamus. Macroscopically the HH are solitary lesions, well-defined round or ovoid soft tissue masses that seems normal brain tissue, that vary in size in diameter, from some millimeters to widespread mixed solidcystic lesions measuring several centimeters (Figure 2A). Calcification, hemorrhage, and necrosis are not common whilst huge lesions often contain well-delineated cysts. Under

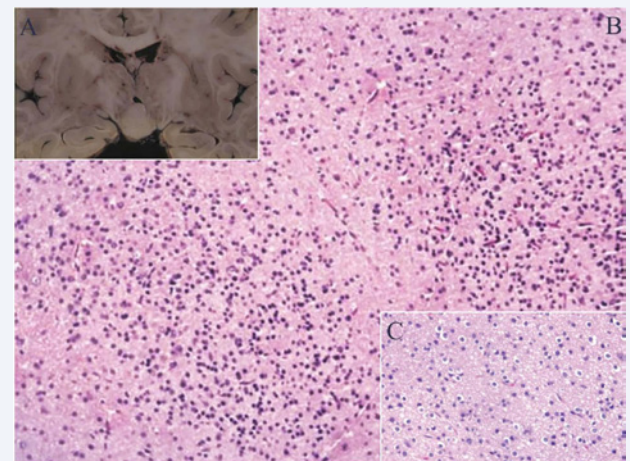


Figure 2 Courtesy of Dr. Ignacio A. Felix. (A) - Coronal section of the brain through the plane of the mammillary bodies reveals a right-side type III HH (B) - Hematoxylin and eosin section through the HH showing cluster of small neurons amongst a background of neuropil-like stroma with individual neurons and diffusely astrocytes between the nodules. Original magnification: 100x. (C) - Higher magnification 400x.

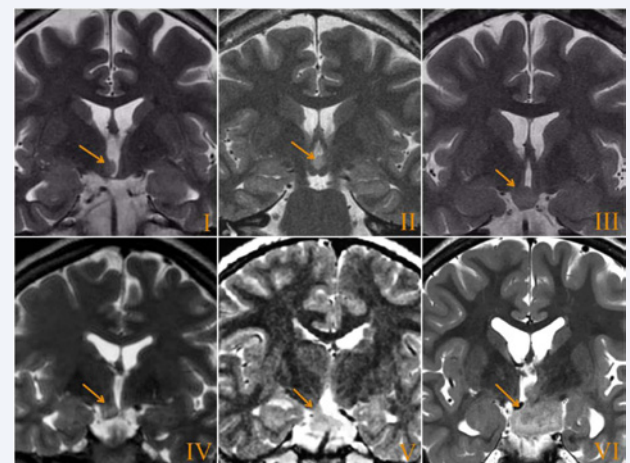


Figure 3 Topological classification of HH [55]. (Type I) - Small HH located inside the hypothalamus extending more or less in the 3rd ventricle. (Type II) - Small lesion and located primarily in the 3rd ventricle. (Type III) - Lesion essentially located on the floor of the 3rd ventricle. (Type IV) - Sessile lesion in the cistern. (Type V) - Pedunculate. (Type VI) - Giants.

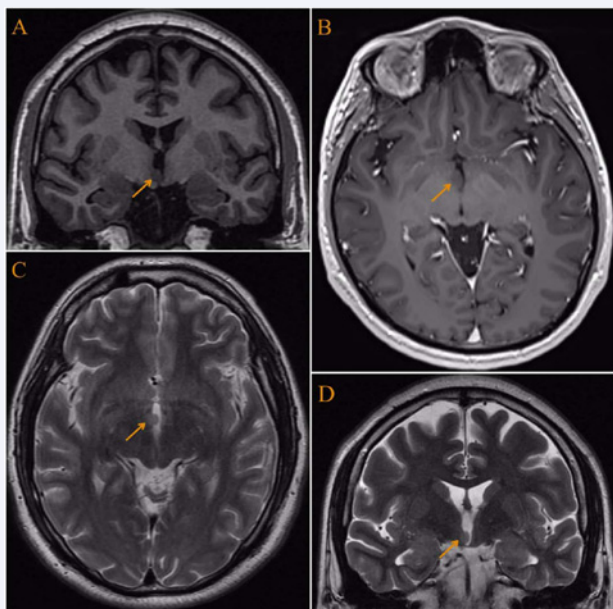


Figure 1 MRI shows a type I hamartoma on the right side of the hypothalamus (small arrows). (A) - Coronal T1WI shows a clearly isointense with gray matter tumor. (B) - Axial T1WI after contrast administration shows a non enhancing lesion. (C) - Axial T2WI shows the mass remains isointense with gray matter. (D) - Coronal T2WI.

the microscope display a HH consist of disorganized networks of well-differentiated small and large neurons interspersed with variable amounts of astrocytes, not very different from respects to other structural lesions associated with other epileptic syndromes. Characteristically presents nodules or neuronal groups [52]. These nodules may vary in size and are composed predominantly of small neurons. A neuropile rich in glia surrounded these nodules with a few interspersed large ganglion cells [19] (Figure 2B and C).

CLASSIFICATION

There have been used several HH classifications based on anatomical features seen on neuroimaging [53]. HH can be

pedunculated or sessile. The former ones are attached to the tuber cinereum and project into the suprasellar cistern. Sessile HH are attached to the floor of the 3rd ventricle and often incorporate the mammillary bodies. Projection into the suprasellar cistern is variable. We use the classification described by Regis et al., which correlates their topology with clinical semiology and its severity, and is especially critical for the selection of treatment [54,55] (Figure 3).

TREATMENT

In appropriately selected patients, HH can be removed completely or they can be completely disconnected from the hypothalamus with an acceptable risk. For several years, the surgical resection appeared to be the best tool to achieve seizure freedom and halting the progressive decline unneurocognitive function, as well as improving the behavior disorders and psychiatric problems in the patients with HH [56]. Nowadays, many centers have adopted minimal invasive techniques, with similar results.

Skull base approaches

Several skull base approaches to type I and large type III and type IV HH are used. Given the familiarity to frontotemporal and pterional approaches this were the first attempts for resection in the initial clinical series [57,58]. Some authors have performed variations in orbitozygomatic, pterional, supraorbital eye brow and subtemporal approaches. The Barrow Neurological Institute have the largest series in surgically treated HH with 165 patients. Of the 165 patients with symptomatic HH, 14 underwent skull base approaches as their initial surgery. Of those 3 patients required a second approach [59]. On their preliminary results [60], 10 patients underwent orbitozygomatic craniotomy, 4 (40%) were seizure free and 4 (40%) had more than 50% reduction in seizures after a mean follow-up of 37 months. Complications included diabetes insipidus, poikilothermia, visual field deficit, and hemiparesis in 1 patient each. Overall, despite excellent outcomes in terms of seizure control the skull base approach resulted in major complications.

Transcallosal interhemispheric approach

Transcallosal approach, is the preferred approach for large HH with significant intraventricular component located superior to the level of the optic tracts. This approach may be used alone to treat large type II lesions. Most of the type III and IV lesions require a staged approach [59]. This approach consists of a small post genua callosotomy followed by midline transseptal dissection and separation of the fornices, which allowed entry through the roof of the third ventricle with subsequent removal and/or disconnection of the HH [61]. It is the preferred approach in younger (≤ 6 years old) patients and in patients with small residual cavum septum. Melbourne et al., report their results after using this technique in 29 patients. They achieved total or near total resection in 18 patients (62%), 15 (52%) were seizure free and another 7 (24%) had a 90% or more decrease in frequency of seizures following surgery with a mean follow-up of 30 months [62]. Complications included thalamic infarction, increased appetite, and short-term memory deficits [63]. In the Barrow group, 47 patients initially underwent transcallosal approach

and eleven patients required subsequent procedures [59]. In the preliminary reports 26 patients underwent transcallosal approach, 14 patients (54%) were completely seizure free, and 9 (35%) had at least a 90% improvement in total seizure frequency. Parents reported postoperative behavior improvement in 23 patients (88%) and in the cognition of 17 patients (65%). Transient postoperative memory disturbances occurred in 15 patients (58%), but persisted in only 2 (8%). Two patients (8%) had persistent endocrine disturbances that required hormone replacement therapy. The mean postoperative follow-up interval was 20.3 months (range 13–28 months).

Endoscopic transventricular approach

Since Akai et al., in 2006 first reported using an endoscope for transventricular biopsy of an HH, many attempts had been made. Endoscopic resection is preferred as the stand-alone surgical treatment for small Type II HH and as a stage in the treatment of small Type III HH [59]. The Barrow group, published 90 patients with endoscopic approaches as their initial surgery. Seven patients had additional procedures [59]. In the preliminary results 37 patients who underwent endoscopic resection 18 (48.6%) were seizure free at last follow-up (median 21 months, range 13–28 months) [59]. The mean postoperative stay was shorter in the patients undergoing endoscopy than in the patients undergoing transcallosal resection (mean 4.1 days' vs 7.7 days, respectively; $p = 0.0006$) [64]. Complications were found in 14 patients, 11 patients had small thalamus infarcts (9 were asymptomatic) and permanent short-term memory loss in 3 patients. Endoscopy is the preferred method but is limited to the size of the ventricle and the size of the tumor. However, patients undergoing endoscopic approaches have shorter hospital stays, and fewer complications than open transcallosal and skull base approaches [65]. Finally individualizing the approach based on the anatomy of the HH and frequently using several approaches in a single patient allowed seizure-free rates in more than 50% of patients treated in the first half of the Barrow group series [59].

Radiosurgery

Stereotactic Radiosurgery (SRS) is an attractive approach that does not require an invasive approach. The main goal of SRS for HH is to deliver doses high enough to affect epileptogenesis without exceeding the tolerance of surrounding structures. Nowadays, modern radiosurgical devices can deliver high dose radiation providing a chance to achieve seizure freedom without hypothalamic or cranial nerve damage. The first successful SRS treatment of HH with seizures was reported by Arita et al., in 1998 [60]. In 2000, the Marseille group reported a series of 8 patients, with 50% cases attaining Engel Class I by Gamma Knife Surgery (GKS), for the 2006, the data were updated, including more than 60 patients who had undergone GKS, with similar improvement results [55]. The meticulous treatment planning and very tight dose distribution are essential to delivering doses without injuring the nearby critical structures. The mean size of HH in the largest series of SRS was 19 mm in diameter, but SRS can be realized in lesions smaller than 30 mm by using steep dose gradients around the target [60], while the size for ideal SRS candidate was reported less than 16 mm [61]. Régis et al., found a clear correlation between dose and efficacy; the marginal

dose was >17 Gy in all patients in whom seizure freedom was achieved and all patients who received <13 Gy showed incomplete seizure control [60]. These studies demonstrate that SRS is an effective treatment for selected patients. Some reports indicated that SRS is as effective as microsurgical resection and safer [55,62]. However, it is important to remember that, like HH microsurgical resection complications, SRS can result also in permanent neurological sequelae [63,64]. Ablashowed that GKS was associated with few complications and about 60% seizure-free rate as part of a multimodal treatment protocol [65]. No serious complication has been reported with SRS but temporary worsening of seizures can be seen as early as 2 months after the procedure. Nevertheless, one of the main disadvantages with SRS is that clinical response can be slow (4-6 months), and the patient remains exposed to the risks of persistent seizures for up to two years after the radiosurgical procedure, early results suggest variable outcomes. Régis et al., reported excellent early seizure response [55]. However, results in terms of long-term seizure freedom are not clear, but, the immediate effect on subclinical discharges turns out to play a major role in the dramatic improvement of sleep quality, behavior, and developmental learning acceleration at school (Figure 4).

Stereotactic radiofrequency thermocoagulation

Stereotactic Radiofrequency Thermocoagulation (SRT) also appears to be an alternative treatment for HH with epilepsy. Brain tissue is coagulated by applying very high frequency alternating current of a depth electrode or a coagulation probe. The volume of a single coagulation is small with a diameter of 4.5-7 mm [66,67], but usually multiple coagulations are applied in a single operative session. A few cases undergoing this treatment have been reported, some of this reports suggested that SRT may be an effective and safe treatment option in selected cases of HH [68]. In 1999, Fukuda et al., reported a single patient with HH treated with

SRT, GS surceased postoperatively and tonic seizures disappeared in the next 4 months. Finally, this patient became seizure free within 14 months [69]. Harvey and Freeman suggested that only 27% of patients with HH who undergo SRT could expect to achieve Engel I or II outcomes [70]. Transient central hyperthermia, hypertension, and tachycardia were observed during SRT. No GS was induced by deep stimulation. Postoperative complications included hyperphagia, hyponatremia, Horner syndrome, short-term memory problems and central hyperthermia after SRT and occurred more frequently compared to an open approach, but in an acceptable manner. These symptoms resolved within one week after surgery after perilesional edema disappeared; no permanent complications were noted [67,68]. The results with SRT, compared with SRS, can be seen immediately following the procedure. SRT seems to be effective for small HH but a long-term study of a large series will be necessary to confirm the efficacy and safety of this treatment [71,72]. Nevertheless, disadvantages of SRT include inexact volume of tissue ablation and the need for multiple trajectories to treat larger HH, thereby adding to the risk of injury to the nearby neurovascular structures compared with a single pass [10].

Stereotactic Laser Ablation

Recently, few centers introduced the Stereotactic Laser Ablation (SLA), positioning as the first line of treatment in some of them [73]. SLA consists of a laser fiber stereotactically inserted with a diffusing tip to cause a thermal lesion while using real-time MRI thermography to monitor temperature and ensure the lesion is restricted to the HH, assessing safety to the surrounding brain tissue [74]. The diffusing tip creates an ellipsoid light distribution along the axis of the 1 cm tip [75]. This novel therapy minimizes the neurocognitive and endocrine adverse effects of open surgery [76] and the rate of seizure freedom appears higher than all other modalities, with potentially lower rates of adverse events. Although, there are only few published reports of SLA for HH. The group at Texas Children's Hospital reported the outcome of the largest series in literature to date, with 14 patients [76]. SLA resulted in 12 of 14 patients with HH becoming seizure-free at a mean follow-up of 9 months. Most importantly, there were no permanent surgical complications, including neurologic deficits and endocrine dysfunction. Brandmeier et al., reported the use of a robot-assisted frameless SLA in a patient with HH with similar rates of success without major complications, although this report is limited to case study [77]. SLA has some advantages compared to other treatment alternatives. One of them is the real-time monitoring by MRI thermometry, allowing a constant evaluation of the thermal energy in the lesion and nearby structures. Currently this is the ablative modality that provides the safest option. In addition, minimally invasive surgery reduces the frequency of surgical complications compared to open and even endoscopic procedures, although there is always the possibility of infection and bleeding with stereotactic procedures, regardless of how small the entry point is. The disadvantages of this therapy are associated with high cost and is not available in most centers. Overall, SLA appears to be a safe and effective treatment for the HH, although further studies are needed to determine its outcomes, side effects and risks, but preliminary evidence is promising.

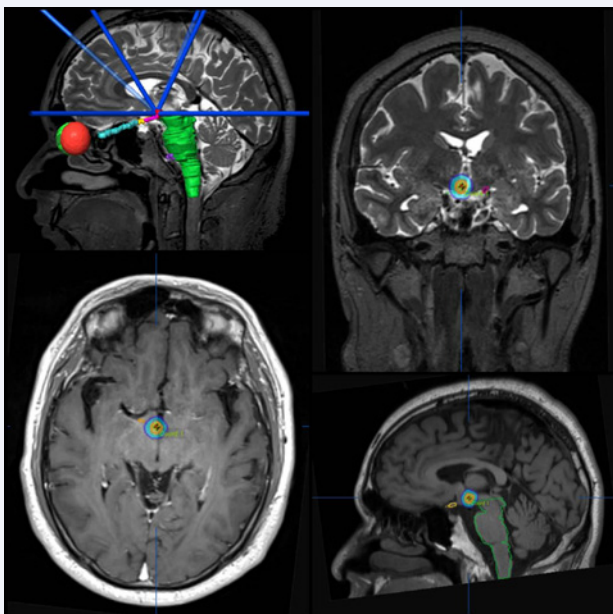


Figure 4 Treatment planning MRI showing right type I HH outlined in sagittal, axial and coronal views. The marginal dose (17 Gy) is displayed in yellow.

DISCUSSION AND CONCLUSION

HH is usually associated with CPP, cognitive impairment, behavior disorders and refractory epilepsy. The clinical presentation of HH and treatment options may be based on its anatomy. The association of the clinical presentation with MRI is mandatory, and the EEG lacks of specificity due to the HH deep location. Neurosurgery plays the most important role in the management and modification of the natural history of the disease. Suitable treatment requires individualization of the approach based on a patient's age and condition, on the anatomy of the HH, and on the surgeon's experience. New minimally invasive techniques such as SRS or SLA are suitable for well-selected patients, with promising results for the control of the epileptic seizures, cognitive, behavior, and endocrinological alterations.

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