INTRODUCTION

Hypothalamic hamartoma (HH), originating from the tuber cinereum or mammillary bodies, are rare non-neoplastic lesion resembling gray matter, composed of hyperplastic neuronal tissue. True incidence is unknown but has been estimated to be from as high as 1 in 100,000 to 1 in 1 million (1).

These lesions are often associated with early onset gelastic seizures, presenting as a well recognized severe childhood epilepsy syndrome. The syndrome is characterized by an early-onset, often in the neonatal period; of brief, repetitive, stereotyped attacks of uncontrollable laughter. These gelastic attacks progress as the patient grows older, with the appearance of other types of seizure. Cognitive deterioration and severe behavioral problems frequently develop later in the first decade of life; together with drop attacks and other clinical and EEG features of secondary generalized epilepsy (2, 3). Patients with gelastic seizures and associated HH often have precocious puberty and progressive mental decline. The seizures are usually refractory to medical treatment. Several studies have demonstrated that the epileptic focus originate from the HH (4). Surgical treatment is required for seizure control and normal development in children. Since publication of seizure reduction with surgical excision in 1969(5), various other
treatments have been tried. In recent years, the interest in the literature for this rare syndrome has increased dramatically.

Surgical removal of the hamartoma, the focal epileptogenic region, has been attempted with variable post-operative outcomes (6, 7). Most neurosurgeons are however reluctant to perform surgery for the peri-hypothalamic lesions because of the high surgical risks. On the other hand, radiosurgery is a noninvasive and valuable procedure for well-defined and deep-seated lesions that are difficult to access by open surgery (8, 9, 10). Radiofrequency ablation was also been tried with the development of image fusion technique. It is used in the initial and palliative treatment. It is less invasive than surgical resection, and the effect is immediate (11). Endoscopic disconnection between the HH and the third ventricular floor improves the refractory seizures without any significant surgical risk (12, 13, 14). Its use has progressed from the small or medium peduncular type to giant type as techniques develops. Seizure freedom is unlikely after vagal nerve stimulation (15, 16). Callosotomy is not a primary surgical choice due to extracallosal diffusion of the generalized seizures from hypothalamic hamartoma (17). Both treatments are thus palliative.

We report our experience in the management of HHs with special reference to symptom profile, surgical procedures and outcome.
REVIEW OF LITERATURE

Historical Perspective of HH

Before approximately 1990, little was known about HH. For the most part a diagnosis was made when imaging studies showed very large lesions thought to be brain tumors within and below the third ventricle. Surgical exploration and biopsy revealed that these masses were composed of normal neuronal elements and glia, and a clear interface between the mass and the native hypothalamus could not be established. The relationship between HH and both isosexual precocious puberty and epilepsy was known, but until the 1980s there were no reports of surgical management except for the abovementioned biopsy. Between 1990 and 2000, case reports on the successful surgical management of HH began to surface. These reports presumably reflected the increasing availability of contemporary imaging techniques. The first CT scanner was installed in the US in 1973. Typical of these reports was an early publication by Machado and colleagues (18) from the Hospital for Sick Children in Toronto. They reported the case of a child with refractory epilepsy surgically treated via the pterional approach. The patient had an excellent outcome, including freedom from seizures and no postoperative morbidity. Interestingly, these authors noted that they found a mass lesion within the
hypothalamus, and its consistency and color were indistinguishable from the native hypothalamus. They stated that the entire mass was removed without difficulty. How these authors decided where to stop the resection was unclear from the operative description; however, the take-home message was that seizures in the context of HH are definitely related to the lesion itself and can be treated or ameliorated by surgical removal of the mass.

There are 2 types of HH and they overlap significantly. Sessile HH lesions with broad-based attachments to the hypothalamus, especially within the third ventricle, are primarily associated with epilepsy and especially with gelastic seizures. On the other hand, HHs that cause isosexual precocious puberty are more likely to be pedunculated lesions that “hang” below the tuber cinereum. Surgical strategies for the latter were more understandable, and soon thereafter the successful treatment of precocious puberty by removing the lesions began to be reported(19,20).

**Clinical presentation**

Patients harboring a HH may present with precocious puberty, developmental delay, and/or epilepsy. HHs may occur either as an isolated sporadic lesion (21) or in association with other anomalies, most commonly in the Pallister-Hall syndrome (PHS) (22). PHS is characterized by HHs, central polydactyly, and other abnormalities including imperforate anus, bifid epiglottis, and panhypopituitarism.
It is inherited as an autosomal dominant, but many cases are due to spontaneous mutations, and is associated with frameshift mutations of the GLI3 gene (chromosomal location 7p13) that functions in the sonic hedgehog pathway. The course of epilepsy in patients is highly variable and tends to be refractory to management with antiepileptic drugs. A majority of patients present in childhood with gelastic seizures, although the diagnosis may be delayed in some cases as a result of a normal electroencephalogram (EEG) [5, 18, 21, 23, 24, 25]. Other seizure types rarely present as the initial epileptic [23]. A majority of children with HHs and gelastic epilepsy may evolve into complex seizures and/or generalized epilepsy, although 25% will not progress and will have a more benign course [26]. Patients who present in adulthood often have milder seizures that are not gelastic and are associated with less severe cognitive and behavioral problems [27].

Gelastic seizures
Laughing seizures were first described by Trousseau (1877) (28). Trousseau described a patient that had a seizure in a regular clinic visit characterized by vertigo and jerking bursts of laughter. When Trousseau asked the patient why he laughed, the patient was surprised with the question because he was not aware during the spell. Trousseau used the term epileptic vertigo for any ‘transient strange phenomena – giddiness, astonishment, ecstasy ... fit of absence’, which he regarded as ‘identical in nature with violent convulsions’. Some years later Gowers
(1881) (29) observed emotions with a cheerful character as a part of a seizure. Daly and Mulder (1957)(30) coined the term “gelastic epilepsy” in 1957. The term comes from the Greek word “gelos” (laughter), to emphasize the main characteristic of these seizures. Gascon and Lombroso (1971) (31) proposed some criteria for gelastic epilepsy including stereotyped recurrence, absence of external precipitants, concomitant manifestations accepted as epileptic, presence of interictal electroencephalography (EEG) abnormalities and absence of conditions that can cause pathologic laughter.

Gelastic seizures are characterized by episodes of laughter [32]. Laughter is typically associated with a facial contraction that resembles a smile [21]. They usually manifest in infancy and usually are the first type to occur in patients with HHs [32,33]. One study demonstrated a mean age of onset of 2.8 years, in which the seizures occurred in over one third of patients [34]. In addition, these seizures have been reported to occur on the first day of life [6, 21, 35, 36, 37, 38, 39]. In infants, the seizures may occur frequently, including episodes during sleep [30]. Adults and older children may have the onset of the urge to laugh that can be suppressed and/or epigastric discomfort in a milder form of gelastic seizures [25,40]. Moreover, dacrysic seizures may occur and manifest with crying and a facial contraction resembling a grimace, and these seizures may occur concomitantly with gelastic seizures [41].
An EEG is frequently normal, and the diagnosis may be delayed. The seizures may be regarded as normal laughter or infantile colic [21,24]. This form of epilepsy is typically unresponsive to antiepileptic drugs, and many children’s gelastic seizures evolve into other seizure types [21,23, 33,34,42].

**Pathophysiology of gelastic seizures**

Many advances have been achieved regarding the pathophysiology of GS in recent years. Currently it is very well known that the HH is the source for the seizures in these patients. The clinical evidence is as follows; a) the production of laughter and GS from the stimulation of the HH with depth electrodes (2, 43) the recording of ictal fast activity from the HH during GS using intracranial recordings (37, 43) the observation of ictal HH hyperperfusion and hypermetabolism with SPECT and positron emission tomography (PET) (36, 37,44), and d) the resolution of seizures with resection, ablation, or irradiation of the HH (3,37,45)

Recent advances have demonstrated intrinsic epileptogenicity of the HH. Two populations of neurons have been shown in HH (small and large neurons). Small neurons are spontaneously firing neurons that express GABA receptors, making them inhibitory in nature (46). The second group is large, pyramidal like neurons that hyperpolarize in repose to GABA agonist. It is proposed that the chronic epileptogenesis of HH is related with the cluster of small GABAergic neurons,
firing action potentials spontaneously and synapse onto the large pyramidal neurons, synchronizing the activity of the large output neurons (47). Alternative theories suggest that the small neurons could have similarities in morphology and function with neurons from lesions of cortical dysplasia, being potentially epileptogenic (46). Also the possibility of ephaptic mechanisms, possibly through gap junction and astroglial involvement has been suggested (46).

**Complex partial seizures**

The evolution of gelastic seizures into complex partial epilepsy usually takes place between the ages of 4 and 10 years old [21]. The patient will have a witnessed impaired level of consciousness, focal motor convulsive features, and automatisms. Children may have an aura in which fear and an epigastric discomfort may occur followed by a search for parental company [23]. It is not uncommon for features of gelastic epilepsy to be retained in complex seizures.

The manifestations of complex seizures will typically lead to a diagnosis of epilepsy in many children, although many patients may have a history of previously unrecognized gelastic epilepsy [23]. The EEG reveals abnormalities, including epileptiform discharges that are localized and intermittent focal slowing [18,34]. The abnormalities may be found over the frontal and temporal lobe areas, which have historically led to unsuccessful focal surgical resections [2, 34].
Generalized epilepsy

Individuals may progress to generalized seizures, including tonic seizures, tonic–clonic seizures, and drop attacks [23,34]. The prevalence of generalized epilepsy in patients with HHs is not precisely known, although some reports have documented them to occur in 70% of individuals harboring these lesions [23,38, 48, 49]. Gelastic or complex seizures typically precede the onset of generalized epilepsy [6, 23,40]. EEG abnormalities are more pronounced along with cognitive and behavioral problems, which can manifest as a consequence of a generalized epileptic encephalopathy [6,21,26, 33,34].

Cognition and behavior

Cognitive impairment and behavioral problems are common in children with epilepsy associated with HHs [32,34,50,51,52]. Speech delay and learning difficulties have been observed. Behavioral disturbances include attention hyperactivity disorders, aggression, angry outbursts, anxiety, and oppositional defiant disorders [52,53].

There have been reports correlating the frequency and severity of seizures with cognitive impairment [50,54]. However, concrete evidence linking neurodevelopment problems, such as cognitive and behavioral disturbances, to epilepsy associated with HHs remains elusive [51,52]. Cognitive impairments have
been demonstrated to occur prior to the start of seizures in a small series of seven children with HHs [7]. Therefore, debate exists as to whether these cognitive and behavioral disturbances occur prior to the onset of epilepsy or is a direct consequence of the seizure activity associated with HHs.

**Precocious Puberty**

Precocious puberty is a clinical finding that has been reported frequently in patients with GS associated with HH. On the other hand, HHs are not associated with other endocrinologic abnormalities such as growth failure, diabetes insipidus, and hypogonadism, in contrast with other hypothalamic pathologies such as astrocytomas, gliomas, and craniopharyngiomas where the frequency is higher. This difference has been explained by the nature of the HH, which is a lesion that has a tendency to displace rather than replace normal structures (6). The association between central precocious puberty and GS was first described in a child who had a hypothalamic tumor attached to the tuber cinereum and mamillary bodies (55). Garcia Morales and colleagues (2007)(56) reported precocious puberty in 3 of 10 patients, Brandberg and colleagues (2004)(15) in 5 of 12 (42%) patients and Fohlen and colleagues (2003) (57) in 5 of 18 (28%). In general, it has been reported between 30% and 40%, but some series have not reported its presence (40). The pathophysiology of precocious puberty has not been established
but some observations have been done. Jung and colleagues (2003) (58) analyzed the localization of the HH and the correlation with the clinical symptoms. Ninety-one percent of HHs in patients with isolated precocious puberty revealed a parahypothalamic position without affecting the third ventricle. Some authors have postulated that the mechanism of precocious puberty in patients with HH is related with the activation of endogenous human luteinizing hormone-releasing hormone gene (LHRH) secretion via astroglial-derived factors and induction of hypothalamic pubertal neuroendocrine function by HH secretion of transforming growth factor (59).

**Pathogenesis and electrophysiology of seizures**

The electrophysiologic basis of gelastic seizures in individuals with HHs has been investigated with an accumulation of evidence pointing toward these lesions as the initial focal site. Previously, it had been difficult to make attempts to elucidate the origin of gelastic seizures because of the deep location of the HHs and normal EEG recordings. Evidence has been derived from the implantation of depth electrodes in patients, which revealed ictal discharges from the HHs during gelastic seizures, and the ability to elicit these seizures with direct stimulation of the implanted electrodes [37,43,60,61]. Studies of surgically resected HH have shown spontaneous pacemaker-like activity in groups of small neurons [47]. Additionally,
positron emission tomography (PET) and single photon emission computed tomography (SPECT) demonstrate hypermetabolism and hyperperfusion in the region of the HH during gelastic seizures [36,37,44].

For complex seizures associated with HHs, EEG typically reveals regional abnormalities [2,34]. It is generally believed that they represent seizure activity spreading from the HH to specific frontal and temporal cortical regions, but thorough investigations have not been conducted to confirm this [62]. It has also been hypothesized that gelastic seizures serve as triggers for rather than propagate complex seizures. Abnormal EEG, ictal SPECT, and interictal PET findings have been demonstrated in the cerebral hemisphere that correlates with the side of attachment of unilateral HH or greater attachment in asymmetric HH [63].

Generalized epilepsy is not well understood in regards to the underlying pathophysiology in patients with HH. It has been hypothesized that the HH serves as a primary generator of epileptiform discharges, which spread to the cerebral cortex and cause the formation of a secondary focus [64,65]. There may be a time period in which the secondary focus of generalized epilepsy remains dependent on epileptic discharges from the HH. This may be evident when the HH is removed with subsequent cessation of seizures. If the generalized epilepsy continues for an extended period of time before removal of the lesion, the secondary focus may
become independent and irreversible in which generalized seizures continue to occur after surgery for the HH. It has been proposed that a propagation of epileptic discharges originates in the HH and extends to the cortex via the mammillothalamic tract. This tract has efferent connections to the anterior thalamus, which has projections to the cingulated gyrus [66,67]. Depth EEG and ictal SPECT studies have provided some evidence for this pathway in the propagation of epileptic discharges [37,43,61]. Palmini et al. reported the attenuation of generalized epilepsy in a HH patient, who had a sectioning of the mammillothalamic tract [38].

**Neuroimaging and classification**

Imaging of HHs typically reveals an abnormality in the region of the tuber cinereum and third ventricle. Computed tomography (CT) may demonstrate a circumscribed lesion that is isodense with the brain. Magnetic resonance imaging (MRI) of the brain is more sensitive and specific than CT. The HH is isointense to gray matter on T1-weighted images and either iso- or hyperintense to gray matter on T2-weighted sequences [68]. In some children presenting with gelastic epilepsy or precocious puberty, small HHs may not be demonstrated on the initial MRI. Subsequent imaging should be performed with thin-section coronal and sagittal MR sequences.
Classification

A classification scheme has been devised for the description of HHs based upon their anatomy [58, 68, 69, 70, 71]. Arita (69) classified into two types according to their topology in relation to the hypothalamus as depicted on MR imaging. Parahypothalamic type in which the hamartoma was suspended from the floor of third ventricle by a peduncle or only attached to the floor and there was no or minimal displacement of the third ventricle. Intrahypothalamic type in which the hamartoma involved the hypothalamus or was enveloped by hypothalamic tissue and distorted the shape of the third ventricle.

Boyko, et al. (68) classified hamartomas into two types, pedunculated and sessile, based on their manner of attachment to the hypothalamus. The pedunculated HHs have a narrow-based attachment to the hypothalamus without any extension into the third ventricle, while the sessile HHs have a broad-based attachment, with or without extension into the third ventricle. The pedunculated HHs have been associated more with precocious puberty, while seizures have been found to be more commonly associated with sessile HHs( 58,68, 69, 70,71). Cognitive decline, developmental retardation, and psychiatric problems, such as rage behavior and mood lability, have been associated with sessile HHs [21].
Valdueza et al. developed a classification scheme that stratifies HHs into types Ia, Ib, IIa, and IIb (Table 1) [71]. This system was based on size, hypothalamic displacement, origin, and site of attachment. Type I tumors usually have a diameter less than 1.5 cm, have a pedunculated attachment to the tuber cinereum or mammillary bodies, and typically are not associated with hypothalamic distortion. Type II tumors are usually larger than 1.5 cm, may have some degree of hypothalamic distortion, and have a sessile attachment to the tuber cinereum or mammillary bodies.

<table>
<thead>
<tr>
<th>Type</th>
<th>Size</th>
<th>Attachment</th>
<th>Origin</th>
<th>Hypothalamic displacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Small–medium</td>
<td>Pedunculated</td>
<td>Tuber cinereum</td>
<td>No</td>
</tr>
<tr>
<td>Ib</td>
<td>Small–medium</td>
<td>Pedunculated</td>
<td>Mammillary body</td>
<td>No</td>
</tr>
<tr>
<td>IIa</td>
<td>Medium–large</td>
<td>Sessile</td>
<td>Tuber cinereum/mamillary body</td>
<td>Slight</td>
</tr>
<tr>
<td>IIb</td>
<td>Medium–large</td>
<td>Sessile</td>
<td>Tuber cinereum/mamillary body</td>
<td>Marked</td>
</tr>
</tbody>
</table>

Delalande and Fohlen proposed a new classification system, which is composed of four categories, for HHs based on the plane of insertion on the hypothalamus (Table 2) [13]. This system was devised in an attempt to facilitate selection of a surgical approach. Type I has a horizontal implantation plane and may be
predominantly lateraled to one side. Type II has a vertical insertion plane and is located within the third ventricle. Type III is a combination of types I and II. Type IV accounts for all giant HHs for which no particular surgical approach can be recommended.

<table>
<thead>
<tr>
<th>Type</th>
<th>Description of attachment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Horizontal implantation plane below floor of third ventricle (parahypothalamic)</td>
</tr>
<tr>
<td>II</td>
<td>Vertical implantation plane within third ventricle (intrahypothalamic)</td>
</tr>
<tr>
<td>III</td>
<td>Combination of I and II (intrahypothalamic)</td>
</tr>
<tr>
<td>IV</td>
<td>Giant lesions (intrahypothalamic)</td>
</tr>
</tbody>
</table>
Delalande and Fohlen classification of hypothalamic hamartomas:-
**Surgical treatment**

Patients harboring HHs and presenting with medically intractable epilepsy, progressive cognitive decline, and/or behavioral problems are usually considered for operative treatment. Surgical intervention offers the patient the best opportunity for eradication of intractable epilepsy and improvement in cognitive function and behavioral problems [3, 48, 72]. The severity of seizures plays a role in the timing of surgery, and early treatment may improve outcomes [32, 73]. Debate exists as to whether complete resection or an anatomical disconnection is necessary to cure patients of their symptoms [1, 6, 14, 38, 57, 74]. A cure has been reported not to occur in some cases of aggressive resection [72, 74]. An incomplete resection or disconnective procedure has been reported to have success in obtaining cures in patients [1, 6, 12, 57, 72]. It has been proposed that disconnection from the mammillary bodies should be the goal of surgery [75].

The surgical approach should be based upon whether the HH is sessile or pedunculated as it relates to the anatomical site of attachment. It has been proposed that sessile HHs should be approached from above and pedunculated HHs from below. HHs have been approached from above through the transcallosal anterior interforniceal technique and below through pterional, orbitozygomatic, supraorbital, subtemporal, and subfrontal lamina terminalis approaches [3, 4, 38, 72, 76, 77]. Based upon the anatomy of the HH, the operative technique should
minimize surgical morbidity. Consideration must be given to critical structures such as cranial nerves, fornices, mammillary bodies, and vasculature, in the vicinity of the HH. Surgical risks include, but not limited to, memory impairment, hypothalamic injury, such as hyperphagia and diabetes insipidus, and vascular injury.

**Pterional approach**

Early approaches to HHs involved the pterional or fronto-temporal techniques [18, 38, 78, 79, 80, 81]. With this approach, a gross total resection is difficult, particularly for sessile HHs with a significant intraventricular component. In addition, the boundary between the hamartoma and hypothalamus may be difficult to ascertain intraoperatively. The working space is limited by the optic apparatus, internal carotid artery, pituitary stalk, and oculomotor nerve. Therefore, this approach is not without the potential for serious complications, such as vascular and/or cranial nerve injuries. In a report of 12 patients, three experienced an anterior thalamic infarct, one had a capsular infarct, and four had an oculomotor nerve palsy [38]. However, two patients became seizure free, and 11 had a greater than 90% reduction in seizures. Delalande and Fohlen reported their results on 14 patients who underwent a pterional approach for HHs with the goal of disconnection [13]. Five patients became seizure free, and seven experienced a greater than 80–90% reduction in seizures, although seven patients needed another intervention for
disconnection. One patient suffered transient hemiplegia as a result of an ischemic injury and a third cranial nerve palsy, and a second patient experienced ischemia of the middle cerebral artery territory resulting in hemiplegia. Based upon their surgical results, the authors formulated a classification system, which was discussed earlier in this report, in an attempt to help select the most appropriate surgical route. They recommended the pterional approach for type I HHs because of a horizontal implantation plane and lateralization. Type III HHs, which are a combination of types I and II, were recommended to be approached through a two-stage procedure, one of which being the pterional craniotomy.

**Orbitozygomatic approach**

The orbitozygomatic approach has been utilized in the resection of HHs [4, 72, 76, 77]. Lesions in the suprasellar region can be accessed through this approach with a wider working corridor. The area of vertical exposure is increased with removal of the orbital rim, which can aid in the surgical resection of pedunculated HHs. In their series of ten patients, in which three underwent the orbitozygomatic approach, Feiz-Erfan et al. achieved gross total and subtotal resections in one and two patients, respectively [72]. Freedom from seizures was achieved in the patient with gross total resection of the HH, while one patient with a subtotal resection had a 75% reduction in seizures. The final patient did not experience any change in seizure frequency.
**Transcallosal anterior interforniceal approach**

The transcallosal anterior interforniceal (TAIF) approach has been described for the resection of HHs from above [3]. Sessile HHs are thought to be best approached through a TAIF since this route is viewed as more favorable with respect to the anatomical attachment of the lesion and allows for direct visualization of the intraventricular component [72]. Frameless stereotaxy can be utilized to select an optimal trajectory to the HH, and a bifrontal–parietal craniotomy can be performed [3]. An incision in the anterior body of the corpus callosum can be made with a subsequent interforniceal approach for entry into the roof of the third ventricle. The entry point is usually anterior to the level of the foramina of Monro. Once access to the area of interest has been obtained, the HH can be extirpated or disconnected. Injury to the fornices with subsequent impairment of short-term memory and endocrine abnormalities are risks of this procedure. In order for the fornices to safely be separated, both leaves of the septum pellucidum must be dissected [82]. Younger patients may tolerate this procedure better than older ones because the leaves of the septum pellucidum have a propensity to fuse with age, which increases the manipulation of the fornices. Feiz-Erfan et al. reported the results of six patients that underwent the TAIF for HHs, in which four had a long-term decline in short-term memory [72]. Additionally, transient diabetes insipidus (DI) occurred in two patients, persistent
DI in one, hypothyroidism in three, transient hyperphagia in two, persistent hyperphagia in one, and transient hyperthermia in five. Despite these complications, five of the patients became seizure free, and one had a significant reduction in seizure frequency. Harvey et al. reported their results in 29 patients who underwent the TAIF approach for HHs [48]. Four patients experienced persistent short-term memory problems, five had hyperphagia, and hypothyroidism occurred in another five patients. Transient hemiparesis occurred in two patients, and 17 experienced transient DI. Fifteen patients became seizure free, and seven experienced greater than 90% in seizure reduction.

**Endoscopy**

Endoscopic approaches to HHs have been utilized for either resection or disconnection [13, 14, 57, 83, 84, 85, 86, 87]. Frameless stereotaxy is used to select the site of the burr hole to allow an optimal trajectory via a transcortical, transventricular route through the foramen of Monro to the interface of the HH [87]. A contralateral approach allows for optimal visualization of the interface between the hypothalamus and hamartoma. This allows for a greater likelihood of disconnection, if not resection of the HH. It has been proposed that this technique be utilized in patients with sessile HHs, which contain an intraventricular component, that are less than 1.5 cm in diameter [87]. Larger sessile HHs can be approached endoscopically if there is 6 mm of clearance to the top of the third
ventricle because adequate visualization of instruments must be a minimum of 6 mm beyond the end of a 30° endoscope [87].

As mentioned previously, Delalande and Fohlen proposed a classification system based upon surgical approaches to HHs, and their series included nine procedures using endoscopy for disconnection [13]. Recently, Ng et al. reported their results in 37 patients treated with endoscopic resection [85]. The median follow-up was 21 months. Twenty-six patients had a greater than 90% reduction in seizures, and 18 of these were seizure free. Eight patients had between a 50% and 90% reduction in seizures, two experienced no change in seizure frequency, and one had a worsening of seizure frequency. Complications included permanent short-term memory impairment in three patients, nine asymptomatic thalamic infarcts, and two symptomatic thalamic infarcts. In those patients with thalamic infarcts, the authors stated that the pial surface of the interpeduncular cistern had been violated, probably disrupting small perforating arteries off the P1 segment of the posterior cerebral artery. The authors compared the efficacy of the endoscopic approach in this series of patients with 26 patients treated via the TAIF approach. In the endoscopic group, 49% of the patients were seizure free compared to 54% in the TAIF group, which was not a statistically significant difference.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of patients</th>
<th>Age range (mean, median)</th>
<th>Procedure</th>
<th>Average procedure length</th>
<th>Follow up</th>
<th>% Seizure free</th>
<th>Precocious puberty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relate et al 2006</td>
<td>44</td>
<td>8 months–44 Y, (15 Y, 10 Y)</td>
<td>Endoscopic via lateral ventricle through foramen on Monroee</td>
<td>60–90 min</td>
<td>12 months</td>
<td>49%</td>
<td>No data</td>
</tr>
<tr>
<td>Ng et al 2006</td>
<td>26</td>
<td>21–24.2 Y (mean 10 Y)</td>
<td>Transcallosal</td>
<td>5–6 h</td>
<td>13–28 (20.3) months</td>
<td>54%</td>
<td>42%</td>
</tr>
<tr>
<td>Relate et al 2006</td>
<td>44</td>
<td>8 months–35 Y (15 Y, 10 Y)</td>
<td>Endoscopic via lateral ventricle through foramen on Monroee</td>
<td>– 90 min</td>
<td>At least 3 months</td>
<td>30%</td>
<td>No data</td>
</tr>
<tr>
<td>Rosenfeld et al 2004</td>
<td>45</td>
<td>29–33 Y (mean 11.3 Y)</td>
<td>Anterior transcallosal transpial interhemispheric approach</td>
<td>Not reported</td>
<td>8–66 months</td>
<td>52%</td>
<td>No data</td>
</tr>
<tr>
<td>Harvey et al 2003</td>
<td>29</td>
<td>4–23 Y (mean 10 Y)</td>
<td>Transcallosal</td>
<td>Not reported</td>
<td>12–70 (mean 30) months</td>
<td>52%</td>
<td>65%</td>
</tr>
<tr>
<td>Freeman et al 2003</td>
<td>12</td>
<td>4–17 Y, (9 Y, 16 Y)</td>
<td>Transcallosal, intermica, transventricular</td>
<td>Not reported</td>
<td>13–61 (mean 29) months</td>
<td>58%</td>
<td>No data</td>
</tr>
<tr>
<td>Dellande and Fohlen 2003</td>
<td>17</td>
<td>9 months–32 Y</td>
<td>One patient total removal (approach not mentioned), 14 ptoral route and 11 endoscopic disconnection</td>
<td>31 min (SD 20 min)</td>
<td>Mean 18.6 months (8 days to 43 months)</td>
<td>47%</td>
<td>29%</td>
</tr>
<tr>
<td>Palmini et al 2002</td>
<td>13</td>
<td>2–33 Y</td>
<td>Perional, or subfrontal</td>
<td>Not reported</td>
<td>1.5 to 6 years  (mean:3.4 years)</td>
<td>15%</td>
<td>31%</td>
</tr>
<tr>
<td>Mottola et al 2001</td>
<td>8</td>
<td>1 week–10 Y</td>
<td>Right fronto-temporal craniomies</td>
<td>Not reported</td>
<td>17 months to 19 year (mean 5 years)</td>
<td>Better control but 0% seizure free</td>
<td>75%</td>
</tr>
<tr>
<td>Rosenfeld et al 2001</td>
<td>5</td>
<td>4–13 Y</td>
<td>Transcallosal</td>
<td>Not reported</td>
<td>9–37 (mean 24 months)</td>
<td>60%</td>
<td>No data</td>
</tr>
</tbody>
</table>
The endoscopic group had a shorter postoperative course than the TAIF group (mean 4.1 vs 7.7 days, respectively), and subsequent permanent short-term memory impairment in patients was comparable between endoscopic and TAIF groups (three and two, respectively). These results provided data that endoscopic resection of HHs may be comparable to the TAIF approach.

Furthermore, Gore et al. reported on a synchronous endoscopic and microsurgical approach for disconnection of a complex HH involving the third ventricle and suprasellar cistern [88]. A supraorbital craniotomy was conducted in conjunction with a transcortical, transventricular endoscopic approach. The endoscope was utilized to disconnect the hamartoma from the hypothalamus, and the subfrontal approach was used to debulk the lesion inferior to the hypothalamus through the opticocarotid cistern. The authors were able to preserve critical structures, such as the optic apparatus, hypothalamic perforating vessels, and infundibulum. The patient experienced a substantial reduction in seizure frequency. Although this is one case report of a HH treated in this fashion, more studies are needed to formulate indications for its use.

**Radiosurgery**

Radiosurgery has been proposed as an alternative, less invasive method for the treatment of HHs (Table 3) [8,12,89,90,91,92,93,94,95]. There is minimal
radiation to surrounding tissues because of the convergence of narrow ionizing beams that are precisely placed through stereotaxy. High conformality and well-delineated dose distributions are vital because important anatomical structures, such as the fornices, optic apparatus, mammillary bodies, pituitary stalk, hypothalamic nuclei, and mammilothalamic tracts, are situated in this region. This treatment modality has been advocated because of the risks associated with surgical resection, including short-term memory problems, hypothalamic dysfunction, and hemorrhage. A disadvantage of radiosurgery is its delayed onset of action. In 1998, Arita et al. published the first case report of effective treatment of seizures associated with a HH after gamma knife radiosurgery [96]. Since this report, a small number of series have been published describing the efficacy and safety of this treatment modality for HHs. The safety profile and efficacy of radiosurgery in a series of HH patients with medically refractory epilepsy were first reported by Regis et al. in 2000 [93]. This was a retrospective study of eight patients, in which four experienced seizure cessation, and the remainder experienced a decrease in the frequency in the number of seizures. There was only one complication whereby a patient experienced transient poikilothermia. Regis et al. also reported their results on the treatment of 30 patients, in which there was a reduction in seizure frequency and eradication of complex partial seizures [45].
Table 4 Selected reports on the outcomes of radiosurgical treatment for hypothalamic hamartomas

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Marginal dose (Gy)</th>
<th>Follow-up (months)</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arita et al. [69]</td>
<td>1</td>
<td>18</td>
<td>21</td>
<td>Seizure free</td>
</tr>
<tr>
<td>Regis et al. [93]</td>
<td>8</td>
<td>12–20</td>
<td>12–71</td>
<td>4 improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 seizure free</td>
</tr>
<tr>
<td>Unger et al. [8]</td>
<td>4</td>
<td>12–14</td>
<td>12–68</td>
<td>Engel II: 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Engel II: 1</td>
</tr>
<tr>
<td>Dunoyer et al. [90]</td>
<td>2</td>
<td>11–14</td>
<td>26–32</td>
<td>Engel I</td>
</tr>
<tr>
<td>Barajas et al. [89]</td>
<td>3</td>
<td>12.5–15</td>
<td>30–50</td>
<td>Improvement</td>
</tr>
<tr>
<td>Mathieu et al. [91]</td>
<td>4</td>
<td>16–20</td>
<td>6–77</td>
<td>Engel II: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Engel III: 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Engel IV: 1</td>
</tr>
</tbody>
</table>

Another series of four patients demonstrated improvement in seizure frequency in two (Engel Class II outcome: 90% reduction in seizure frequency), transient improvement in one (Engel Class III outcome: 75% reduction in seizure frequency), and no effect in another (Class IV outcome: no effect of treatment or minimal improvement) [91]. The authors did not report any complications related to the treatment with radiosurgery. A report by Dunoyer et al. reviewed the efficacy of radiosurgery in two HH patients with a follow-up of 26 and 32 months, respectively, and demonstrated an Engel class I outcome (cessation of seizures) in both patients. There were no complications documented. Barajas et al. provided
data showing partial improvement in three patients treated with stereotactic radiosurgery without any complications, and reports on the follow-up of four patients after radiosurgery by Unger et al. demonstrated a progressive decrease in both seizure frequency and intensity [8, 89]. In the report by Unger et al, three patients had an Engel II outcome, and one had an Engel III outcome [8].

These limited studies provide data that radiosurgery can have some efficacy in the treatment of intractable epilepsy in patients with HHs. Cumulatively, the studies reported a reduction in seizure frequency and intensity in most patients, but epilepsy was reported to have ceased in less than 50%. Very few complications have been reported, making it a safe, minimally invasive treatment modality. The target volume and radiation dose still need to be optimized for treatment protocols and given the limited studies radiosurgery has been advocated for patients with mild to moderate symptoms or for salvage therapy [93, 97]. A subset of patients with mild forms of epilepsy, mild behavioral problems, and/or mild cognitive decline may be good candidates for radiosurgery as the initial treatment modality. With further refinement in the radiosurgical parameters needed to treat HHs with maximal efficacy and further studies providing documentation of favorable results, treatment paradigms will be developed with radiosurgery as a key component.
**Interstitial brachytherapy**

The stereotactic implantation of temporary radioactive $^{125}\text{I}$ seeds in HHs has been utilized as another treatment modality $[^{98},^{99}]$. These radioactive seeds emit gamma radiation with minimal delivery to normal surrounding structures. This is an invasive procedure since normal brain has to be traversed for the placement of the seeds. Moreover, seed implantation may be difficult for very firm HHs. Schulze-Bonhage et al. reported their results in six patients without any complications $[^{79}]$. Two patients achieved seizure freedom, and there was only persistence of auras in two. Three patients with only mild improvement in seizure control underwent seed reimplantation, and there was subsequent improved seizure control in two of these patients. Another report by Schulze-Bonhage et al. on stereotactically implanted radioactive $^{125}\text{I}$ seeds in 15 patients described significant improvement in seizure frequency in 53% of patients $[^{99}]$. Transient headaches and mental slowing were related to the development of local edema. Persistent hyperphagia occurred in three patients.

Recently, the results of 24 patients with HHs and gelastic epilepsy treated with $^{125}\text{I}$ seeds were reported $[^{100}]$. The mean follow-up period was 24 months, and a majority of patients tolerated the treatment well. Nine patients had an Engel I outcome, four with Engel II, four with Engel III, and seven with Engel IV. The authors’ data demonstrated that the duration of epilepsy prior to interstitial
radiosurgery had a negative impact on outcome and increased the risk for cognitive side effects. Four patients experienced persistent weight gain. No neurological deficits or abnormal hormone levels were detected, except for an elevated prolactin in one patient.

**Radiofrequency ablation**

Stereotactic radiofrequency ablation has been used in the treatment of HHs with some success [11, 60, 101, 102]. Homma et al. reviewed a series of five patients treated from 1997 to 2004 [101]. The patients underwent MRI-guided targeting of their HHs with subsequent radiofrequency thermocoagulation between the normal hypothalamus and hamartoma. The goal of the treatment was to achieve a disconnective effect. Seizure freedom occurred in three patients with significant improvement in the remaining two. There were no permanent neurologic or endocrine abnormalities, postoperatively.

**Vagal nerve stimulation**

Vagal nerve stimulators have been used to treat children with a variety of seizure disorders and have generally been reserved for those with medically intractable seizures and are not candidates for epilepsy surgery. Murphy et al. reported their experience with vagal nerve stimulator implantation in six patients with HHs [16].
Three patients experienced 25%, >50%, and >90% reduction in their seizures, respectively. Four patients had an improvement in their behavior. Interestingly, one patient experienced a greater than 90% increase in seizures. Although this small study provides some limited data that is favorable, more extensive studies are needed to assess the efficacy of vagal nerve stimulation in the treatment of medically intractable epilepsy associated with HHs.
AIMS AND OBJECTIVES OF THE STUDY

To study the symptom profile and outcome of treatment of hypothalamic hamartoma treated at our centre.
MATERIAL AND METHODS

We retrospectively studied twenty two patients who had MR imaging diagnosis of HH, treated at our centre between 1998 and 2010. All patients underwent neurological examination, endocrinological and neuropsychological assessment, scalp electroencephalography assessment, video-electroencephalography recording, and magnetic resonance imaging scan. For each patient, data on clinical feature, neuroimaging characteristics, number of antiepileptics used, surgical approach, histopathology report, postoperative symptom relief, complication after surgery were collected. Our inclusion criteria was (i) MRI diagnosis of hypothalamic hamartoma, (ii) histopathology report suggestive of hypothalamic hamartoma in operated patients, (iii) minimum follow up of 12 months was considered as prerequisite for inclusion in the study.
RESULTS

Out of 22 patients, 19 patients were included in this study. Three patients were excluded, HPR of that patient was glioma.

A) Demographic Profile:-

1) Gender- Out of 19, 12 were male and 7 were female.

![Figure 1: Sex distribution of study population](image)
2) **Age profile:** The age were ranged from 2 yr - 28 yrs (mean age 14.28 yrs).

![Figure 2: Age profile of patient](image)

3) **Age of onset of seizure:**

The age of epilepsy onset ranged from the 20 days of life to 13 years (mean 3.27 yrs). The age of hypothalamic hamartoma diagnosis was 2 yr - 27 yrs (mean age 11.03 yrs). The follow up period was from 1 yr to 11 yrs (mean 3.82 yrs).
B. Symptoms profile:

The symptoms profile were seizure (16 patients), seizure with precocious puberty (2 patients), precocious puberty only (3 patients), behavioural disturbances (8 patients), visual disturbances (1 patient), developmental delay (2 patients), neuropsychological impairment (10 patients). Seizure types were gelastic seizures (GS), complex partial seizure (CPS) and generalized tonic clonic seizure with secondary generalization. Three patients experienced gelastic seizure, two experienced complex partial seizure and eleven experienced GS,
CPS, GTCS. Seizure frequency ranged from 1-50/week. The numbers of antiepileptic drugs were tried in patients ranged from two to five. The hormonal profile like FSH, LH, Estradiol, Progesterone, testosterone thyroid function test were done in patient who had precocious puberty
C. Radiological Feature:-

Neuroimaging was performed in each patient; the radiological features consisted of the detection of a diencephalic-sited nonevolutive nonenhancing lesion, isointense on T1-weighted images and hyperintense on T2-weighted images. Hypothalamic hamartoma size ranged from 4mm to 25 mm. Hypothalamic hamartoma, in which presenting feature seizure, were nine (Type I) and seven (Type II). All three patient with precocious puberty had pedunculated hypothalamic hamartoma hanging from floor of third ventricle.
D. Surgical Approach:-

Thirteen patient operated for hypothalamic hamartoma out of which 10 for refractory seizure and 3 for precocious puberty. The six patient managed medically and kept on follow up because seizure was in controlled and not disabling. Out of six, two lost follow up one year, in one patient surgery planned, three patient seizure partially controlled and not disabling.

The surgical approach used as trancallosal interforniceal (TcIf), endoscopic (3), Pterional transylvian (PtTs) for seizure. Total seven patient underwent pterional approach.

Figure 6: Different surgical approach used in seizure patient
Out of these, 5 patient underwent pterional craniotomy only, transcallosal and pterional surgical approach used in two patient, and one patient underwent two times pterional approach. The patient who underwent two times pterional, one time operated at other places. The reoperation was done in three patient.

E. Complication:-

The complication in transcallosal approach were hyponatremia, diabetes insipidus and complication in pterional approach were 3rd nerve plasy, diabetes
insipidus, hemiparesis, infarct in left caudate and putamen. In endoscopic approach, there was no complication.

Table 5 – Approaches and its complications

<table>
<thead>
<tr>
<th>Approach</th>
<th>Complication</th>
<th>No. of patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcallosal interforniceal</td>
<td>-Hyponatremia</td>
<td>-1</td>
</tr>
<tr>
<td></td>
<td>-Diabetes insipidus</td>
<td>-1</td>
</tr>
<tr>
<td></td>
<td>-Memory disturbances</td>
<td>-not assessed</td>
</tr>
<tr>
<td></td>
<td>-hemiparesis</td>
<td>-0</td>
</tr>
<tr>
<td>Pterional Transsylvian</td>
<td>-3rd nerve palsy</td>
<td>-2</td>
</tr>
<tr>
<td></td>
<td>-Diabetes insipidus</td>
<td>-1</td>
</tr>
<tr>
<td></td>
<td>-hemiparesis</td>
<td>-1</td>
</tr>
<tr>
<td></td>
<td>-infarct in caudate and putamen</td>
<td>-1</td>
</tr>
<tr>
<td></td>
<td>-EDH</td>
<td>-1</td>
</tr>
<tr>
<td>Endoscopic</td>
<td>-Thalamic infarct</td>
<td>-0</td>
</tr>
<tr>
<td></td>
<td>-short –term memory loss</td>
<td>-0</td>
</tr>
<tr>
<td></td>
<td>-hemiparesis</td>
<td>-0</td>
</tr>
</tbody>
</table>

EDH - extradural hemorrhage
### Table 6: Profile of Operated HH Patients for seizure

<table>
<thead>
<tr>
<th>S.N.</th>
<th>Age (yr)</th>
<th>sex</th>
<th>Preop Engel class</th>
<th>HH type (delalande &amp;fohlan)</th>
<th>No.of operation</th>
<th>Surgical approach</th>
<th>Postop Engel class</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>M</td>
<td>IV</td>
<td>II</td>
<td>1</td>
<td>TcIf</td>
<td>I</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>M</td>
<td>IV</td>
<td>I</td>
<td>1</td>
<td>Pt.Ts.</td>
<td>III</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>M</td>
<td>IV</td>
<td>II</td>
<td>1</td>
<td>Endoscopic disconnection and partial excision</td>
<td>I</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>M</td>
<td>IV</td>
<td>II</td>
<td>1</td>
<td>Endoscopic near total excision</td>
<td>II</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>M</td>
<td>IV</td>
<td>I</td>
<td>2</td>
<td>TcIf,Pt.Ts.</td>
<td>IV</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>M</td>
<td>IV</td>
<td>I</td>
<td>2</td>
<td>Pt.Ts</td>
<td>I</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>M</td>
<td>IV</td>
<td>II</td>
<td>3</td>
<td>TcIf,Endoscopic ,Pt.Ts.</td>
<td>III</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>M</td>
<td>IV</td>
<td>II</td>
<td>1</td>
<td>Pt.Ts.</td>
<td>IV</td>
</tr>
<tr>
<td>9</td>
<td>25</td>
<td>M</td>
<td>IV</td>
<td>II</td>
<td>1</td>
<td>Pt.Ts.</td>
<td>I</td>
</tr>
<tr>
<td>10</td>
<td>13</td>
<td>F</td>
<td>IV</td>
<td>I</td>
<td>1</td>
<td>Pt.Ts.</td>
<td>I</td>
</tr>
</tbody>
</table>

- TcIf-transcallosal interforniceal, PtTs-pterional transsylvian
F. Symptom Profile Outcome:-

After surgery, all patient with seizure except two showed clinical improvement. In all three patient with precocious puberty only, thelarche, menarche, pubic hair and other secondary sexual character disappeared and they are doing well till last follow up. The two patient who had seizure with precocious puberty, in one patient precocious puberty not improved but became seizure free after surgery .that patient receiving GnRh analogue therapy. Other patient already received GnRh analogue before he came to our institute, no precocious puberty feaure was present. In all patient pterional approach used and gross total decompression was done.In Post op MRI was done in two patient there was no residual.The complication were hemiparesis and 3rd nerve paresis(1 patient) which improved gradually and diabetes insipidus (2 patients).

After surgery eight patient (80%) showed clinical improvement, two patients (20%) have continued to have seizures with same frequency at last follow up. In particular ,5 patient (50%) became seizure free(Engel Class I) and 2 patient (20%)showed 50% seizure control(Engel Class III), one patient (10%) showed more than 90 % seizure control(Engel class II). The patients, who had
Table 7: Profile of operated HH patients for precocious puberty

<table>
<thead>
<tr>
<th>S.N.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Symptom Preop.</th>
<th>Hormone profile (HP)</th>
<th>Post op.outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>GS</td>
<td>PP</td>
<td>GS</td>
</tr>
<tr>
<td>1</td>
<td>2&amp;1/2</td>
<td>F</td>
<td>N</td>
<td>Y</td>
<td>Abnormal</td>
</tr>
<tr>
<td>2</td>
<td>2&amp;1/2</td>
<td>F</td>
<td>N</td>
<td>Y</td>
<td>abnormal</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>F</td>
<td>N</td>
<td>Y</td>
<td>Abnormal</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>M</td>
<td>Y</td>
<td>Y</td>
<td>abnormal</td>
</tr>
</tbody>
</table>

- Y=yes, N=no, GS-gelastic seizure, PP-precocious puberty, HP-hormone profile

continued seizure, had residual in postop MRI. One patient who underwent endoscopic disconnection and partial excision became 100% seizure free. One patient who underwent endoscopic near total decompression showed 90% seizure control. The seven patient (70%) underwent pterional approach (either first or second surgery), out of which three patient(Engel Class I) became almost seizure free, two patient have 50% seizure controlled(Engel Class III), two patient continued to have seizure (Engel Class IV). Three patient underwent interhemispheric transcrallosal approach one(33.3%) became seizure free(Engel
class I), two (66.6%) continued to have seizure with same frequency (Engel class IV).

These two patients post op MRI after first surgery showed residual lesion. Then these two patient underwent pterional approach, one patient seizure controlled more than 50% (Engel Class III), one patient continued to have same frequency.
DISCUSSION

Hypothalamic hamartoma (HH) is a rare entity and collective experience of several centers has to be evaluated to reach meaningful conclusion in establishing management protocols.

The scientific literature available on hypothalamic hamartomas is limited to small series of surgically managed patients and case reports. Considerable debate still exists on the indications for surgical treatment and optimum surgical approach. Correlation between size of the hypothalamic hamartoma and symptoms is not clear. The location of the lesion is a crucial and difficult surgical terrain making the access tedious and cumbersome. Complete and safe resection is often not feasible and more than one surgical approach may be required.

Demographic profile

Tassinari C.A et al demonstrated a mean age of onset of 2.8 years (range 1 day to 15 yrs) (34). In addition, these seizures have been reported to occur on the first day of life (21, 35, 36). In our study, the age of epilepsy onset ranged from 20 days of life to 13 years (mean age 3.27 yrs).
Symptom profile

Gelastic seizures usually manifest in infancy and usually are the first type to occur in patients with HHs (32, 33). Only rarely other type of seizure are first manifestation. In our study, gelastic seizure is first type of seizure in almost all type of patient. Gradually gelastic seizures evolve into multiple seizure types — complex partial seizures with or without secondary generalization in 35.5%, tonic–clonic seizures in 15.1%, tonic seizures in 17.7% and atonic seizures in 33.3% (34). Patients in our series also have CPS and generalized epilepsy. Sometimes patient of HH may presents with precocious puberty which has been postulated to be caused by an interruption of normal inhibitory pathways that results in the autonomous pulse release of GnRH. In our series four patients presented with features of precocious puberty and one patient had past history of precocious puberty which had resolved with GnRH treatment.

Indication of surgical treatment

Patients harboring HHs and presenting with medically intractable epilepsy, progressive cognitive decline, behavioural problems and/or medically refractory precocious puberty are usually considered for operative treatment. Surgical intervention offers the best opportunity for eradication of intractable epilepsy, improvement in cognitive function and behavioral problems [3,48,72] as well as
precocious puberty regression. The severity and duration of seizure are related to surgical outcome and early treatment may improve outcomes [32, 73]. Only a few reports have described control of GS with medication (27, 33), but in general all the studies have shown that patients with gelastic seizure eventually become intractable to medication (15, 103). In our study, almost all patients were intractable to antiepileptic drugs, in few patient some type of seizure controlled with medication. Although precocious puberty can be managed with medical treatment, potential concerns include drug related side effects, the possibility of further growth of the hamartoma, and high cost of treatment.

Optimum surgical approach

No single approach is the best approach or is appropriate in all cases. Adequate surgical treatment requires individualization of the approach based on a patient’s age the anatomy of the HH, associated surgical risks and the surgeon’s experience. It is becoming increasingly clear that a 1-stage approach to all HHs is probably inappropriate. Based upon the anatomy of the HH, the operative technique should minimize surgical morbidity. Consideration has to be given to critical structures such as cranial nerves, fornices, mammillary bodies, and vasculature, in the vicinity of the HH.
The transcallosal interforniceal approach has been preferred approach for large HHs with a significant intraventricular component. This approach can be used alone to treat large Type II lesions and many Type III and IV lesions which require a staged approach. The major problem of these approaches is the frequent injury of fornices. Rosenfeld and colleagues (3) proposed to reach the HH from above by performing a transcallosal interforniceal approach and complete or nearly complete (95%) excision of the HH was achieved for all patients with no adverse neurological, psychological, or visual sequelae. This surgical approach has shown a significant better seizure control. Feiz-Erfan et al (72) used transcallosal and interforniceal approach in 6 patients, out of which five became seizure free and in one patient seizure significantly reduced. Harvey and colleagues (48) in series of 29 patients achieved seizure freedom in 15 and greater than 90% reduction in seven patients by using this approach. In our study, three patient underwent interhemispheric transcallosal approach, one (33.3%) became seizure free (Engel class I), two (66.6%) continued to have seizure with same frequency (Engel class IV).

Several skull base approaches to Type I, III, and IV HH are used. Pterional approach was favoured in the early approaches to HHs due to surgeon familiarity. The advantage is that it provides the shortest most direct route to the hamartoma. The disadvantage is the need to maneuver most important
neurovascular structures—internal carotid artery, optic nerve and tracts, oculomotor nerve and pituitary stalk thereby limiting access. Lesions with a significant intraventricular component are usually difficult to resect via this route. Furthermore, given the narrow operative corridor, despite neuronavigation, it may be difficult to identify the boundaries of the lesion particularly if there is a broad attachment to the hypothalamus and mamillary bodies. Palmini et al. [38] in a series of 12 patients operated via pterional route and had subtotal or complete resection. He achieved seizure freedom in three, with six having a greater reduction. Delalande and Fohlen [13] advocate a disconnection of the intraventricular component without resection. Seizure freedom was achieved in five patients and greater than 80–90% seizure reduction in seven with the majority having improvement in behavior. In our study, seven patient (70%) underwent pterional approach (either first or second surgery), out of which three patient (Engel Class I) became almost seizure free, two patient have 50% seizure controlled (Engel Class III), two patient continued to have seizure (Engel Class IV). The complication in pterional approach were 3rd nerve plasy, diabetes insipidus, hemiparesis, infarct in left caudate and putamen which is comparable with other authors.

Endoscopic approaches to HHs have been utilized for either resection or disconnection [13,14,83] and is preferred as the stand-alone surgical treatment for small Type II HHs and as a stage in the treatment of small Type III HHs. Recently,
Ng et al. reported their results in 37 patients treated with endoscopic resection [85]. Complications included permanent short-term memory impairment in three patients, nine asymptomatic thalamic infarcts. We also used in three patients for endoscopic resection and disconnection. In our study, one patient had undergone endoscopic near total resection. Patient had greater than 90% reduction in seizure.

Complication

Based upon the anatomy of the HH, the operative technique should have minimize surgical morbidity. Consideration must be given to critical structures such as cranial nerves, fornices, mammillary bodies, and vasculature, in the vicinity of the HH. Surgical risks include memory impairment, hypothalamic injury such as hyperphagia and diabetes insipidus, hemiplegia or hemiparesis, endocrinological disturbances, cranial nerve palsy like 3rd CN and vascular injury. Complications reported with transcallosal approach are short-term memory impairment most common, third nerve paresis, hemiparesis(49), appetite stimulation and weight gain, transient hypersomnia and hyperthermia (3,49) and transient endocrine abnormalities such as hypothyroidism and diabetes insipidus (3,72). Higher levels of cranial nerve damage and cerebrovascular accidents have been associated with pterional approaches(38). The complication in our study were hyponatremia, 3rd nerve palsy, diabetes insipidus, hemiparesis, infarct in left caudate and putamen. Memory disturbances could not be assessed.
Symptoms outcome after surgery

Harvey and colleagues (48) report the seizure outcome of 29 patients with a mean follow up of 30 months using transcallosal approach. He achieved seizure freedom in two, with four having a greater than 90% reduction, eight patients having less than 50% improvement. Results from the 2 largest series using transcallosal approach have demonstrated seizure freedom in 14 (54%) of 26 patients (49) in 1 series and 15 (52%) of 29 patients (3) 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. Palmini et al (38) achieved seizure freedom in three, with six having a greater than 90% reduction. The largest series of patients who have undergone endoscopic resection of their hamartomas is from the Barrow Institute (85), and seizure freedom was attained in 18 (49%) of 37 patients. In our series, one patient who underwent endoscopic disconnection and partial excision became 100% seizure free. One patient who underwent endoscopic near total decompression showed 90% seizure control. The seven patient who (70%) underwent pterional approach (either first or second surgery), out of which three patient (Engel Class I) became almost seizure free, two patient have 50% seizure controlled (Engel Class III), two patient continued to have seizure (Engel Class IV). Three patient underwent interhemispheric transcallosal
approach 33.3% patient became seizure free (Engel class I). In our study, out of 10 operated patients five became seizure free, 90% seizure controlled in one, more than 50% seizure controlled in two patients.

In 1967, Northfield and Russell (80) were the first to describe the surgical resection of HHs for treatment of precocious puberty and since then there have been a number of cases reported in which excision of the hamartoma has been achieved safely and has resulted in regression of this condition (19, 68, 104). Recent reports have been more positive, with Boyko, et al. (68) reporting of three patients, and Albright and Lee (19, 104) reporting of five where total resection of an HH reversed the endocrinological features of precocious puberty. Because total resection of the hamartoma appears to be necessary for a good endocrinological result, effective surgical treatment is limited to those lesions that are pedunculated and thus more amenable to total removal. In our series, 4 patients had precocious puberty and all of them underwent gross total resection and showed good results.
**Disconnection versus resection**

Debate exists as to whether complete resection or an anatomical disconnection is necessary to cure patients of their symptoms [1,6,14,38,57,74]. There are multiple possible routes by which seizures spread from the HH into adjacent and remote parts of the brain. One pathway is that the seizures spread directly through the mammillary body to the thalamus and beyond via the mammillothalamic tracts(6) so that disconnection of the HH from the mammillary body has become one of the key goals of the disconnection surgery. Sessile HHs are attached to one or both mammillary bodies(75). The intrinsic epileptogenic activity and stable nature of the HH support the rationale of blocking the epileptic spreading pathway to control GS. Delalande and Fohlen (13) have considered that surgical disconnection, instead of surgical resection of the HH, is an effective and safe alternative. The disconnection is performed by endoscopic and/or pterional approach depending on the plane of insertion of the HH on the hypothalamus (13). A cure has been reported not to occur in some cases of aggressive resection [72, 74]. An incomplete resection or disconnection procedure has been reported to have success in obtaining cures in patients [1, 6, 12, 57, 72]. It has been proposed that disconnection from the mammillary bodies should be the goal of surgery [75]. Procaccini and colleagues (86) reported a series of 33 patients who underwent
disconnection by pterional and/or robot-assisted endoscopic approach. All patients except one improved clinically. Seizure freedom (Engel Class 1) was seen in 16 patients (48.5%) and significant improvement (Engel Classes 2 and 3) in 16 patients (48.5%). Patients who only required endoscopic disconnection had better control of seizures; thus, 90% of them were seizure free (Engel Class 1) and 10% showed significant improvement (Engel Class 3). In our study, one patient had undergone endoscopic disconnection surgery and subsequently patient was seizure free.

**Extent of resection versus outcome**

Efficacy for seizure control also correlated with the extent of surgical resection of the hamartoma. Patients undergoing 100% resection were more likely to be seizure free in comparison to those who had subtotal resection. The mean percentage of HH resection correlated positively with the likelihood of complete seizure control. Feiz-Erfan et al (72) used transcallosal and interforniceal approach in 6 patients, out of which five became seizure free and in one patient seizure significantly reduced. All seizure free patients were undergone gross total resection and one patient who had seizure frequency underwent subtotal resection. Our study showed that patients, who had gross total resection of hypothalamic hamartoma, were more likely to be seizure free in comparison to who had subtotal resection and residual on postop magnetic resonance imaging.
<table>
<thead>
<tr>
<th>S.N</th>
<th>Authors</th>
<th>No. of pts.</th>
<th>Age range (mean)</th>
<th>Procedure</th>
<th>Follow up</th>
<th>% seizure free</th>
<th>Precocious puberty</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Rosenfield et al 2001(3)</td>
<td>5</td>
<td>4-13yr</td>
<td>Transcallosal</td>
<td>9-37 months</td>
<td>60%</td>
<td>No data</td>
</tr>
<tr>
<td>2</td>
<td>Mottolese et al 2001(76)</td>
<td>8</td>
<td>1week-10yr</td>
<td>Right frontotemporal craniotomies</td>
<td>17 montms-19 yr</td>
<td>Better control but 0% seizure free</td>
<td>75%</td>
</tr>
<tr>
<td>3</td>
<td>Palmini et al 2002(38)</td>
<td>13</td>
<td>2-33yr</td>
<td>Pterional or subfrontal</td>
<td>1.5 to 6 yrs</td>
<td>15%</td>
<td>31%</td>
</tr>
<tr>
<td>4</td>
<td>Delalande and Fohlan 2003(13)</td>
<td>17</td>
<td>9month s-32yr</td>
<td>Pterional endoscopic</td>
<td>8 days to 43 months (mean 18.6 months)</td>
<td>47%</td>
<td>29%</td>
</tr>
<tr>
<td>5</td>
<td>Freeman et al 2003(6)</td>
<td>12</td>
<td>4-17yr</td>
<td>Transcallosal interforniceal</td>
<td>13-61 (mean 29)months</td>
<td>58%</td>
<td>No data</td>
</tr>
<tr>
<td>6</td>
<td>Harvey et al 2003(48)</td>
<td>29</td>
<td>4-23yr</td>
<td>Transcallosal</td>
<td>12-70(mean 30)months</td>
<td>52%</td>
<td>65%</td>
</tr>
<tr>
<td>7</td>
<td>Ng et al 2006(49)</td>
<td>26</td>
<td>2.1-24.2yr</td>
<td>Transcallosal</td>
<td>13-28(20.3)months</td>
<td>54%</td>
<td>42%</td>
</tr>
<tr>
<td>8</td>
<td>Rekate et al 2006(76)</td>
<td>44</td>
<td>8month s-44yr</td>
<td>Endoscopic via lateral ventricle through formen of monro</td>
<td>12 moths</td>
<td>49%</td>
<td>No data</td>
</tr>
<tr>
<td>9</td>
<td>Our series 2011</td>
<td>13</td>
<td>2-28yr</td>
<td>Transcallosal interforniceal, pterional, endoscopic</td>
<td>1yr-11yr</td>
<td>50%</td>
<td>75%</td>
</tr>
</tbody>
</table>
**Limitation of study**

The study being retrospective and dealing a very rare pathological entity is a small series of patients but still has meaningful implication. There is a certain heterogeneity in the symptom, demographic and radiological class of lesion in these patients and hence statistical analysis comparing different surgical approaches and medical versus surgical treatment is not feasible.

However this study should inspire a collaboration and pooling of collective experience from various centers so that management guidelines can be defined for this rare lesion. A large randomized control study to decide the best surgical approach as per the radiological subtype of the hamartoma and also resection versus disconnection randomization would be ideal and is proposed.
CONCLUSION

Hypothalamic hamartoma is a rare pathological entity causing refractory seizures, precocious puberty and behavioural dysfunction. Indications for surgery include medically refractory seizures, medically refractory precocious puberty and behavioural disturbances. No single approach can be considered optimum for surgical resection. The suitable surgical approach is determined by size and radiological grading. More than one surgical approach may be required for optimum resection. Completeness of resection correlates with best symptom relief including optimum seizure outcome.
Preoperative MR-imaging of hypothalamic hamartoma

Postoperative MR-imaging of the same patient

H and E stain: Neuronal predominance with diffuse microarchitecture
REFERENCES


special reference to gelastic epilepsy and surgery. Neurosurgery 34:949–958, discussion 958


Proforma

Name-
A/S-

Hosp.No.-
Contact no.-
Address-
Age of diagnosis-

Seizure profile-

Type-
Age of onset-
Frequency/month

Associated symptoms-
Endocrinological-
Visual disturbances-
Behavioural disturbances-
Others-
Investigation:-

EEG-
VEEG-
MRI-size-
Type-(Delalande & Fohlen classification)-

Neuropsychological:-

Hormonal profile:-

Treatment-

Antiepileptic drug-

name of drug-

No.of drug-

Dose:-

Operation:- 1st surgery:-

Approach-

Complication:- Major:-

Minor-

Reoperation:-

Follow up:-

Duration :-

Seizure outcome (Engel classification):-

1st:- Seizure profile-

  type-

  frequency-

  AED-

  Neuropsychological:-
2\textsuperscript{nd}:-

3\textsuperscript{rd}:-

last follow up:-

Imaging postop:-MRI-(extent of resection):-

partial- (<50\%)-

Total(100\%)-

Near total (90-100\%)-

Subtotal(50-90\%)-