Clinical characteristics and long-term outcome of surgery for hypothalamic hamartoma in children with refractory epilepsy

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Abstract

Context: Hypothalamic hamartomas (HH) are ectopic masses of neuronal and glial tissue most commonly presenting with medically refractory gelastic seizures with evolution to other seizure types. They are also associated with cognitive and behavioral problems to varying extent. Surgery has been found to improve quality of life in more than 50% of patients. **Aim:** To evaluate the clinical characteristics and long-term outcome of surgery in children with HH and refractory epilepsy. **Materials and Methods:** A retrospective analysis of presurgical, surgical, and postsurgical data of six children who underwent surgery for HH and had at least 3 years follow-up was performed. **Results:** Six children (male: female = 5:1) aged 3-16 years (at the time of surgery) underwent surgical resection of HH for refractory epilepsy. At last follow-up (range 3-9 years), three children were in Engel's class I, two in Class II, and one in class III outcome. Significant improvement in behavior, quality of life was noted in four children; while the change in intelligence quotient (IQ) was marginal. **Conclusions:** Medically refractory epilepsy associated with behavioral and cognitive dysfunction is the most common presentation of HH. Open surgical resection is safe with favorable outcome of epilepsy in 50% with significant improvement in behavior and marginal change in cognitive functions.

Key Words

Gelastic seizures, hypothalamic hamartoma, refractory epilepsy, surgery

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Introduction

Hypothalamic hamartomas (HH) are developmental malformations of the inferior hypothalamus in the region of the tuber cinerium and mammillary bodies.[1] The clinical presentation is varied and includes intractable seizures, precocious puberty, and behavioral and cognitive disturbances. In majority of cases, epilepsy begins during the neonatal or early childhood period, usually in the form of gelastic seizures. In majority of patients, epilepsy evolves into drug-resistant epilepsy, manifesting with multiple seizure types and progressive cognitive and developmental deterioration. Freedom from seizures occurs in more than 50% patients undergoing microsurgical or endoscopic resection/disconnection of HH. Such patients also have significant improvement in behavior, cognition, and quality of life following surgery. Alternatively, less invasive methods like stereotactic radiosurgery and radiofrequency ablation under stereotactic guidance have shown promising results.[2] In the present study, we discuss the clinical characteristics and long-term postsurgical outcome of six children with refractory epilepsy and HH.

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Materials and Methods

Retrospective analysis of presurgical, surgical, and postsurgical data was performed in six children with HH and refractory epilepsy. The patients were evaluated for refractory epilepsy and accounted for 1.33% of the epilepsy surgeries performed. Data pertaining to patient's demography, clinical presentation, hormonal assessment, imaging characteristics, seizure semiology, interictal and ictal electroencephalogram (EEG) findings, and neuropsychology was analyzed. The outcome measures were postoperative seizure remission (according to Engel's outcome) and improvement in behavior, cognition, and quality of life. Binet Kamath test was used to assess intelligence in children, while adolescents were

assessed using Wechscler's adult intelligence performance scale and battery of cognitive tests. The impact of surgical intervention on patient's quality of life was studied with a quality of life in epilepsy (QOLIE) 10 questionnaire. The assessments were performed at 3 months, 1 year postsurgery, and once in a year thereafter.

Results

Six children (five males and one female) with medically refractory seizures underwent resection of HH. Patient's age at surgery ranged from 3 to 16 years.

Clinical features

Seizures were the presenting feature in all the children. Onset of epilepsy was before the age of first year in all boys and at 2 years age in one girl. Gelastic seizure was the clinical presentation in all six children with a mean age of onset of 5.5 months. One child had a combination of gelastic and dacrystic seizures. Daily seizures were noted in five and weekly in one. One patient had history of recurrent status epilepticus (nine times) prior to surgery with poor quality of life. None had family history of epilepsy. Five had multiple types of seizures. Precocious puberty was noted in four boys. One child had hypothyroidism. None of the others had any hormonal disturbances. Three children had developmental delay. Behavioral problems including hyperactivity were noted in five children; three boys had features of attention deficit hyperactivity disorder (ADHD) [Table 1]. The intelligence quotient (IQ) was normal in three and below average in the rest. The quality of life was poor in five. Four children could never go to school due to high seizure frequency.

Presurgical evaluation

The magnetic resonance imaging (MRI) brain showed sessile HH in one and pedunculated in five children (giant HH in one) [Figures 1 and 2]. During video EEG, multiple types of seizures (automotor, hypomotor, and partial with secondarily generalized) were recorded in five and only gelastic and hypomotor seizures in one child. One child aged 4 years, with a giant HH had a combination of gelastic and dacrystic seizures. The interictal EEG showed generalized and multifocal epileptiform activity with no clear cut lateralization in five and right temporal spikes in one child. The ictal onset showed bitemporal rhytmic theta in three, generalized high voltage spike and sharp wave activity in two, and regional right temporal onset in 1. Ictal single-photon emission computed tomography (SPECT) with ethylcysteinate dimer (ECD) was performed in three, which showed bitemporal hyperpperfusion in two and right temporal hyperperfusion in one.

Surgery

Subtotal resection of HH was done in all. Three children underwent resection by pterional approach and two by transcallosal approach. One child underwent resection through pterional approach and had no significant improvement in seizure frequency and second resection was performed through transcallosal approach. None had postsurgery complications. Acute postoperative seizures were noted in one child.

Postsurgery outcome

The follow-up ranged from 3.2 to 9.6 years. At 1 year follow-up, four children were in Engel's class I outcome (two seizure free and two were having occasional auras), while two children were in Engel's Class II outcome [Table 2]. However, at last follow-up (mean 6.4 years), three children were in Engel's class I and two in Class II outcome. One patient who underwent surgery at 16 years age was in Class III. However, his seizure frequency decreased by 30% with no events of status epilepticus requiring hospitalization. At last follow-up, all children showed marginal increase in intelligence (change of IQ by 2-10 points). Improvement in behavior and ADHD was noted in four children, while one child had persistent ADHD features. The change in IQ and improvement in behavior was noted at 1 year and maintained during follow-up. Quality of life improved in four children who resumed their academic activities. Two children continued to have poor quality of life because of persistence of behavioral problems in one and high seizure frequency in the other.

Discussion

Patients harboring a HH may present most often in childhood with gelastic seizures and/or precocious puberty or developmental delay. The course of epilepsy in these patients is highly variable and tends to be medically refractory. Without surgical intervention, the gelastic seizures may progress to complex partial and/or generalized epilepsy, although 25% continue to remain the same.[3,4]

Gelastic seizures, which are characterized by episodes of laughter, are characteristic of HH and usually manifest in infancy. Dacrystic seizures may also occur concomitantly in these patients, manifesting with crying and a facial contraction resembling a grimace. In our series of six patients, gelastic

Table 1: Clinical characteristics of patients who underwent surgery for hypothalamic hamartomas

Patient	Age (years)	Sex	Seizure characteristics		IQ before surgery	Behavioral problems	QOLIE
			Age of onset	Semiology			
1	16	Male	2 months	Gelastic, hypomotor, automotor, partial with secondarily generalized	58	Present	Poor
2	12	Female	2 years	Gelastic, automotor	89	None	Good
3	3	Male	4 months	Gelastic, automotor, hypomotor	85	ADHD	Poor
4	4	Male	6 months	Gelastic, dacrystic, automotor	66	ADHD	Poor
5	9	Male	5 months	Gelastic, automotor	82	ADHD	Poor
6	11	Male	6 months	Gelastic, automotor, epileptic spasms	52	Present	Poor

IQ = Intelligence quotient, QOLIE = Quality of life in epilepsy, ADHD = Attention deficit hyperactivity disorder

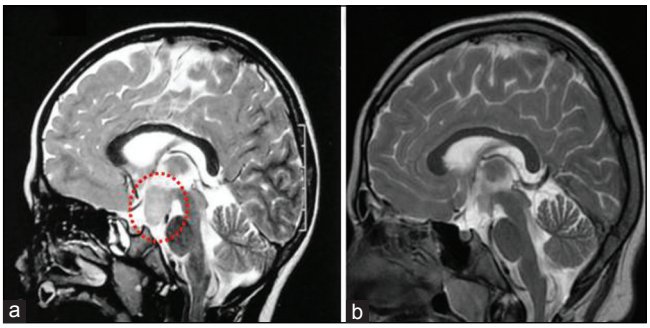

Figure 1: T2-weighted (T2W) sagittal images of a patient showing a pedunculated variety of hypothalamic hamartoma. The preoperative image is shown on the left with the lesion encircled (a). The postoperative image following surgical resection is shown on the right (b)

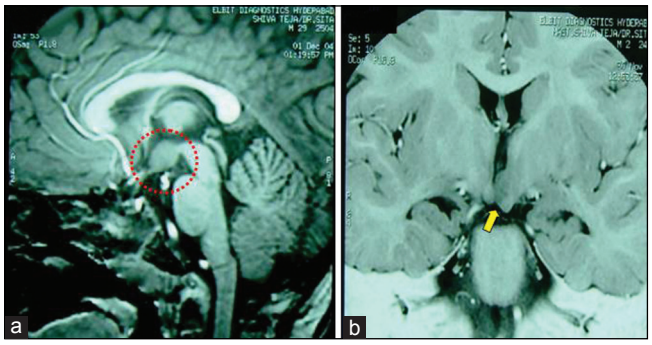

Figure 2: Preoperative T1W images following gadolinium administration showing a sessile variety of hamartoma seen attached to the tubercinerium on sagittal images (a) and to the mammillary body on coronal images (b)

Table 2: Surgical outcome of patients at last follow-up

Patient	Seizure outcome (Engel's class)	Number of AEDs at last follow-up	IQ change	Behavior	QOLIE
1	III	3	58 to 59	No change	Poor
2	I	None	89 to 98	Normal	Attending school
3	IC, auras	2	85 to 90	Improved	Attending school
4	II	3	66 to 69	ADHD persisting	Poor
5	IC, auras	None	82 to 89	Improved	Attending school
6	II	2	52 to 58	Improved	Attending school

IQ = Intelligence quotient, QOLIE = Quality of life in epilepsy, ADHD = Attention deficit hyperactivity disorder, AED = Antiepileptic drug

seizures were the initial presentation in all the six children; while one child had a combination of gelastic and dacrystic seizures. Untreated or partially treated gelastic seizures may progress to complex partial seizures between the ages of 4 and 10 years. These are characterized by automatisms, hypomotor activity, loss of awareness with the surroundings, and may be preceded by an aura of fear or epigastric discomfort. Complex partial seizures may be the initial presentation of patients with HH, although many patients may have a history of previously unrecognized gelastic epilepsy on evaluation. Generalized seizures (including tonic seizures, tonic-clonic seizures, and drop attacks) are known to occur in 70% of individuals harboring HH.[5] Gelastic or complex partial seizures typically precede the onset of generalized epilepsy. All the children in the present series had multiple types of seizures.

Till date, controversy exists about attributing cognitive and behavioral disturbances to the direct consequence of the seizure activity associated with HH. Behavioral disturbances include ADHD, aggression, angry outbursts, anxiety, and oppositional defiant disorders. Speech delay and learning difficulties have also been observed.[6] In our series, three children had ADHD features and two had behavioral disturbances. The IQ was below average in three. HHs are usually isointense to grey matter on T1WI, iso- to hyperintense on T2WI, and do not enhance after Gadolinium administration. They may be sessile or pedunculated depending on their attachment to the hypothalamus and extension into the third ventricle. Pedunculated or parahypothalamic ones have a narrow attachment to the hypothalamus without any extension into the third ventricle. The sessile or intrahypothalamic variety refers to HH with a broad-based attachment with or without extension into the third ventricle. Seizures are more commonly associated with sessile variety and precocious puberty is seen more often in the pedunculated variant. Cognitive and behavioral disturbances are more common in the sessile type.[7] We encountered only one case of sessile HH in our series of six patients. Three out of five patients with the pedunculated variety had precocious puberty as a clinical presentation.

Surgery offers the best opportunity for remission of intractable epilepsy and improvement in cognitive function and behavioral problems associated with HH. Although it is debatable as to whether complete resection or an anatomical disconnection is needed for achieving seizure control and improvement in patient's cognition and psychology, it has been proposed that disconnection from mammillary body should be the goal of surgery.[8,9] It is recommended that sessile HH be approached by a transcallosal, interforniceal route and pedunculated HH by one of the following approaches: Pterional, orbitozygomatic, supraorbital, subtemporal, or a subfrontal lamina terminalis approach.

In our series, three patients achieved Engel's class I outcome after surgery, while two patients were in Engel's class II and one in class III remission at the last follow-up. All children showed minor improvement in intelligence after surgery. Neuropsychology improved in two out of three children with preexisting behavioral problems. In the two largest series of patients reported by Ng *et al.*,[10] and Rosenfeld and Feiz-Erfan,[11] patients who underwent open surgical resection had seizure freedom rates of 54% (in a series of 26 patients) and 52% (in a series of 29 patients) after a mean follow-up of 20

Table 3: Comparison of various treatment modalities for hypothalamic hamartomas

Treatment modality	Seizure freedom	Indications	Comments
Microsurgery a. Transcallosal, interforniceal b. Pterional/ orbitozygomatic approach	52-66%	Large HH with a significant intraventricular component located superior to the level of optic tracts HH with horizontal implantation plane, lateralized on to one side	Immediate improvement of symptoms Factors favoring a transcallosal approach include younger age (interforniceal dissection becomes difficult with advancing age), HH with bilateral attachment and presence of residual cavum septum Major advantage is that it provides the most direct surgical route to suprasellar cistern and HH
Endoscopic disconnection (stereotactic guidance)	49%	Small, intraventricular HH with a unilateral, vertical plane of attachment; the HH is approached through the contralateral foramen of Monro	Advantages: HH is approached via foramen of Monro without disturbing the fornix. Postoperative recovery period is short Stereotactic guidance is needed to localize the lateral ventricle and foramen of Monro as well to plan the trajectory for disconnection
Radiosurgery	37% after a delay of 6-12 months	Small primary and secondary (residual) HH; preferred in adolescent and adults with intact memory and milder epilepsy as well as in select patients with bilateral mammillary body attachment	Latency period for epilepsy control to be achieved. Potential injury to optic pathway is a concern. Risk to memory is lower compared with microsurgery
Radiofrequency ablation	Isolated case reports	Primary treatment of small HH and management of residual lesions	Minimally invasive, low risk approach with immediate results. Disadvantages include imprecise volume of tissue ablation and requirement of multiple trajectories for larger lesions which increases risk of injuring adjoining structures
Combined modalities		Larger lesions depending on extent of resection or disconnection, seizure remission achieved with initial treatment	Individualization of approach is based on patient's age, size, and anatomy of HH and surgeon's experience

and 30 months, respectively. An additional 35% and 24% of patients, respectively had > 90% reduction in seizures. Younger age, shorter duration of epilepsy, smaller volume of HH, and completeness of resection were associated with a likelihood of freedom from seizures; while type of seizure and developmental delay had a negative correlation with outcome of surgery with respect to seizure freedom. Subjective improvement in behavior and cognition were reported by parents in 88% and 58% of patients within the first few weeks after surgery.[10] We noted significant improvement in behavior in all children with improvement in quality of life and marginal improvement in IQ. We did not perform any statistical analysis as more number of patients will be required. Other treatment options available for management of HH include open surgical disconnection, endoscopic resection/disconnection, stereotactic radiosurgery, radiofrequency ablation, interstitial brachytherapy, and vagal nerve stimulation.[8-26] Ng *et al*., reported the largest series of patients who have undergone endoscopic resection of HH with a seizure freedom of 49% after a minimum period of 1 year follow-up.[12] The improvement in seizures following radiosurgery with gamma knife or linear accelerator follows a temporal sequence with an early favorable response followed by transient worsening and reduction/remission of seizures thereafter. The marginal dose delivered to the tumor varied from 11 to 20 Gy in different series. Regis *et al*., reported a 37% seizure freedom with a significant improvement in another 22% of their 27 patients treated with gamma knife.[13] The advantages with radiosurgery are the option of repeating the same in patients who do not respond to initial therapy and the choice of surgical resection after upfront radiosurgery for larger lesions.

A comparative analysis of various treatment modalities for HH is shown in Table 3.[8-26] Microsurgery has the highest success rate and should be the primary treatment option in an era where there is an increasing trend towards combined modalities of treatment.

Conclusion

HH is a cause of medically refractory gelastic seizures which may progress to other seizure types. Favorable outcome after surgery was achieved in 50%. Subjective improvement in behavior was noted in four children supporting the concept of 'reversible cognitive dysfunction' in these patients. However, no significant change in IQ was noted postsurgery at long-term follow-up.

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