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Surgical treatment of hypothalamic hamartoma

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Abstract

Hypothalamic hamartomas are often associated with early onset gelastic seizures, precocious puberty, behavioral problem and suboptimal response to antiepileptic drugs. Until now, four surgical options have been reported to reduce seizure by >50%. Surgical excision have good seizure outcome but postoperative complications were not infrequent, whether by pterional or transcallosal interforaminal approach. Radiosurgery is noninvasive alternative to resective surgery but the effect usually does not appear until several months later. Radiofrequency ablation is less invasive than surgical resection and its effect is immediate, but lacks long term follow-up data. It also requires three dimensional analysis of the lesion to enhance efficacy and safety. As hypothalamic hamartoma is intrinsically epileptogenic and epileptogenic discharges spread from the lesion, blocking the seizure propagation through endoscopic disconnection is regarded as an effective and safer option. Surgical choice for a particular patient should take into account the hamartoma's size, location, surgeon's preferences, possible complication as well as the effect and risk of the various surgical methods. In the present review, open surgery, endoscopic disconnection, radiosurgery and radiofrequency ablation are discussed.

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.¹ True incidence is unknown but has been estimated to be from as high as 1 in 50-100,000² to 1 in 1 million.³

These lesions are often associated with early onset gelastic seizures, presenting as a well-recognized, severe childhood epilepsy syndrome.⁴ The syndrome is characterized by an early-onset, often in the neonatal period; of brief, repetitive, stereotyped attacks of uncontrollable laughter.⁴ 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.^{5,6} Patients with gelastic seizures and associated HH often have precocious puberty and progressive mental decline.^{5,6} The seizures are usually refractory to medical treatment. Several studies have demonstrated that the epileptic focus originate from the HH.^{7,8} Surgical treatment is required for seizure control and normal development in children. Since publication of seizure reduction

with surgical excision in 1969⁹, various other treatment has been tried. In recent years, the interest in the literature for this rare syndrome has increased dramatically.¹⁰

Surgical removal of the hamartoma, the focal epileptogenic region, has been attempted with variable post-operative outcomes.^{11,12} 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.^{10,13-20} 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.²¹ Endoscopic disconnection between the HH and the third ventricular floor improves the refractory seizures without any significant surgical risk.²²⁻²⁴ Its use has progressed from the small or medium peduncular type to giant type as techniques develops.²³⁻²⁵ Seizure freedom is unlikely after vagal nerve stimulation.^{26,27} Callosotomy is not a primary surgical choice due to extracallosal diffusion of the generalized seizures from hypothalamic hamartoma.²⁸ Both treatments are thus palliative. In the present review, open surgery, endoscopic disconnection,

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radiosurgery and radiofrequency ablation will be the main focus. (Table 1)

MICROSURGERY

Surgical removal of hypothalamic hamartoma has been reported in the literature since 1969.⁹ Resection through subfrontal, transylvian, subtemporal, or supratemporal pterygial regions have been reported or suggested in the literature. A number of complications have occurred, including thalamocapsular infarctions with hemiplegia, transient third nerve palsies, diabetes insipidus, and hyperphagia.⁶ Postoperative complications was the main reason for resistance to this treatment.

Surgical excision has previously been the standard treatment to control the seizures. Although there was no evidence of the epileptic focus being in the HH, many surgeons have tried to resect the HH and, in doing so, have achieved partial control of the seizures.^{11,29,30} On the other hand, a classification system has been proposed which takes into account the size, location, attachment, and effect of the lesion on the hypothalamus.³¹ HH can have either pedunculated or sessile attachments to the hypothalamus. These factors have a significant effect on the resectability of the lesions. Unfortunately, pedunculated HH, which is easily resectable, is usually asymptomatic or only associated with precocious puberty.³¹ Many reports of surgical cases indicated that total or near total resection is very important in achieving seizure control.^{11,12,30,32-35} Some reports insist that HH attached to the mammillary body or tuber cinereum is easily resectable without surgical risks.^{11,12} However, total resection is very difficult to achieve because the HH resembles the normal gray matter, despite the existence of hyperplastic neuronal tissue. Most neurosurgeons are still reluctant to perform surgery for perihypothalamic lesions, because of the high risks.

Classic pterional approach for HH may be suitable for lesions protruding into the interpeduncular cistern. If the lesion extends into the third ventricle, complete removal of tumor is difficult in this approach. Palmini *et al.* report good seizure control in this approach. Four of 11 patients had 3rd nerve palsy with full recovery in 3.³⁵ Transcallosal interforaminal approach was introduced by Rosenfeld *et al.*³⁶ This approach makes use of more anterior trajectory that can minimize dissection and retraction of the column of fornix. Prospective study of 26 patients shows good seizure control, with 54% seizure free and

21% reduction of seizure frequency³⁷, achieving good seizure outcome and modest complication. Peduncular type is easier than sessile type for surgical excision. They did not report surgical mortality, but oculomotor palsy, hemiparesis, meningitis and communicating hydrocephalus. In very large HH, transcallosal interforaminal approach is proposed but with significant risks of impaired short-term memory.³⁸

GAMMA KNIFE SURGERY

Arita *et al.* in 1999 reported the first case of HH successfully treated with gamma knife surgery.²⁰ This is a 25-year-old man with 24 years history of gelastic and tonic clonic seizures. Regis *et al.* in 2000 reported very good safety and efficacy result from radiosurgery¹⁷ in their retrospective series of 8 patients. Prospective trial of gamma knife surgery in HH shows that gamma knife is as effective as microsurgical resection, and very much safer.³⁸ Gamma knife surgery also avoids the vascular risk related to radiofrequency lesioning or stimulation.³⁸ The disadvantage of radiosurgery is its delayed response as compared to other surgical methods.

Stereotactic radiosurgery is a neurosurgical approach whose efficacy is now well established, as well as low morbidity in cases of well-defined and deep-seated lesions that are difficult to access by resective surgery.²³ The radiation dose necessary to eliminate epileptogenesis is still under debate. Some researchers report that the minimum doses that suppress the epileptic focus in experimental settings range from 10 to 20 Gy with collimators of 4-18 mm in diameter, and are lower than those producing tissue necrosis.³⁹⁻⁴¹ Others reported that radiation doses of 10-15 Gy were sufficient to reduce cortical activity and extinguish the seizure focus originating from the HH.⁴² Regis *et al.* reported that the marginal dose was more than 17 Gy for all patients in the successful group and less than 13 Gy for all patients in the "improved" group.¹⁷ However, higher marginal doses might injure critical surrounding structures such as the optic pathway, hypothalamus and subthalamus. The concern of inducing radiation optic neuropathy can influence both patient selection and dose selection in radiosurgical treatment.²³ In general, radiosurgery is a noninvasive alternative to resective surgery in case of recurrence of tumor, large sessile tumor and failed previous surgery or poor general condition for surgery. However, there is still risk of damaging the surrounding

Table 1: Comparison of different surgical treatments for hypothalamic hamartoma

| | Microsurgery | | | | Radiofrequency ablation |
|--------------------|---|---|---------------------------------------|--|---|
| | Pterional | Transcallosal interformiceal | Endoscopic disconnection | Gamma knife surgery | |
| Seizure outcome | Good | Good | Good | Poor | modest |
| Invasiveness | +++ | +++ | + | - | + |
| Effectiveness | Immediate | Immediate | Immediate | Delayed | immediate |
| Type | Peduncular | Peduncular | Peduncular> Sessile | Peduncular | Sessile |
| Size | All | All | Small and medium All in peduncular | Small and medium | Small and medium |
| Longterm follow up | +++ | - | - | + | + |
| Complication | +++ 3 rd nerve palsy, hemiparesis, visual loss, hyperphagia, diabetes insipidus 1969 ⁹ | ++ 3 rd nerve palsy, hemiparesis, memory loss, meningitis, hydrocephalus 2001 ³⁶ | + | + | + |
| Reported | | | 2002 ³² | 1998 ²⁰ | 1999 ⁵¹ |
| | | | | Transient worsening of the epilepsy, poikilothermia | 3 rd nerve palsy, brain stem infarction |

structures. The appropriate dose of irradiation has yet to be established. The effect usually does not appear until several months or years. It should be used with caution in intractable seizures in young children who are still undergoing development. When the first irradiation is ineffective, a second treatment should only be carried out after 36 months.³⁸

STEREOTACTIC RADIOFREQUENCY ABLATION

Stereotactic radiofrequency lesioning has been used for the treatment of movement disorders, epilepsy, intractable pain, and metastatic brain tumors.⁴³⁻⁴⁵ To minimize the risk, preoperative simulation and strict localization of the targets are mandatory.⁴⁶ Image fusion techniques has been shown to be useful, as it can avoid the effects of image distortion and enhance the accuracy of stereotactic co-ordinates.⁴⁷⁻⁴⁹ Radiofrequency ablation appear to be effective in reducing the epileptogenic potential of the lesion and improve the epilepsy control. It is less invasive than surgical resection, and its effect is immediate.²¹ Sessile HH often causes intractable epilepsy, which is difficult to control by microsurgical resection, endoscopy and gamma knife surgery, especially when the hamartoma is intrahypothalamic, large, or irregularly shaped.^{21,25} Radiofrequency ablation can be used for initial and palliative therapy as in radiosurgery. However, the lack of long-term follow-up data, and the lack of established intraoperative monitoring methods for ablated area restricts its application as initial treatment. Due to irregular conformation and close proximity to the normal hypothalamus, mammillary bodies and visual pathways, direct lesioning with a stereotactic probe carries a potential risk.³⁸ The debate has now shifted to the best means of treatment with a variety of surgical approaches, and the likelihood of destroying the lesion with radiofrequency probes or gamma knife surgery.⁵⁰

ENDOSCOPIC DISCONNECTION

Akai *et al.* reported a case of decreased seizure frequency after neuroendoscopic biopsy with partial removal of HH followed by linear accelerator stereotactic radiosurgery.³² They underwent second surgery combining pterional and neuroendoscopic partial resection due to relapse seizures after transient improvement.³² After second surgery, atonic and gelastic seizures disappeared. Delalande and Fohlen reported that disconnection between HH and the third ventricle

floor by open or endoscopic surgery improved the refractory seizures without posing significant risk.²⁵ Choi *et al.* placed depth electrode in the HH, and showed that the epileptic discharges spread from the lesion, thus confirming that HH is intrinsically epileptogenic.²⁴ Blocking the propagation of discharges by endoscopic disconnection is safer and more effective than other treatment modality.²³

The depth of disconnection can be determined by preoperative T1- and T2- weighted coronal MRI scans, and by depth electrode monitoring.^{23,24} Neuronavigation system also helps to determine the confines of the protruding HHs and the normal hypothalamus by direct visualization.²³ Complete disconnection can be confirmed by observing air density in the prepontine cistern on postoperative CT scan and with T1- and T2-weighted coronal MRI scans.²³

Disconnection between HH and third ventricle using neuroendoscopy can avoid large craniotomy, and is easy to achieve in small peduncular type. However, large sessile type IV HH is very hard to treat using only disconnection. Additional procedures such as radiosurgery, repeated endoscopic surgery, and open surgery should be considered in such cases.²⁴

In summary, transventricular neuroendoscopic approach to the hypothalamus is less invasive and more effective than radical surgery or radiosurgery. Neuroendoscopic surgery can therefore be one of the treatments of choice for hypothalamic hamartoma.

OTHER SURGICAL TREATMENTS

In the reports on vagus nerve stimulation for HH, none of the patients achieve seizure freedom after the procedure.^{26,27} This indicates that vagus nerve stimulation is less effective than radiosurgery, endoscopic disconnection, or microsurgery, where almost all patients improve with more than 50% are seizure-free. It should be a palliative procedure. As for callosotomy, the efficacy is very limited, surgical risk is high, and there is no beneficial impact on behavior and psychiatric symptoms.²⁸ The poor response to callosotomy suggests extracallosal diffusion of seizures from HH.²⁸ Both vagal nerve stimulation and callosotomy should not be initial surgical treatment choice for HH.

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