

Transcallosal resection of hypothalamic hamartomas in patients with intractable epilepsy

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ABSTRACT – A variety of surgical treatments for intractable epilepsy with hypothalamic hamartoma (HH) are described, although most are derived from limited patient experience gathered from several centres. We describe the results of transcallosal resection of HH in 29 consecutive patients undergoing surgery at one centre.

Twenty-nine patients aged 4-23 years (mean 10 years) underwent HH surgery with a minimum of 12 months follow-up. A comprehensive, presurgical epilepsy evaluation, supplemented with endocrine and ophthalmological assessments was performed in all cases. HH were resected via a transcallosal, interforniceal approach to the third ventricle, with the assistance of frameless stereotaxy, limiting the resection to the margins of the third ventricular walls and floor and minimising traction and diathermy.

Complete or near-complete (> 95%) resection of the HH was achieved in 18/29 patients, 75-95% resection was achieved in seven patients (four of whom had complete or near-complete disconnection of residual HH) and less than 50% resection was achieved in four. Postoperatively (follow-up 12-70 months, mean 30 months), 15 became seizure-free (nine off antiepileptic medication), seven had > 90% reduction in seizure frequency, three had 55-80% reduction in seizure frequency, and four had less than 40% reduction in seizure frequency. Of 16 patients who had seizures in the early postoperative period, six became seizure-free. No patient or lesion characteristics were associated with postoperative seizure freedom, including features of symptomatic generalised epilepsy. Neurobehavioural improvement and resolution of EEG abnormalities were seen in the majority. Complications were transient hemiparesis in two, transient hypernatraemia in 17, short-term memory impairment in 14 (persistent in four), weight gain in ten (persistent in five), need for supplemental thyroxine in five, and lowered growth hormone (uncertain clinical significance) in six.

Transcallosal resection of HH is an effective treatment for intractable epilepsy, with 76% patients in our series being seizure-free or having > 90% seizure reduction. The operative risks include stroke, short-term memory disturbance, weight gain and minor endocrine disturbances. Based on published data, the transcallosal approach appears to be safer and more effective than other operative strategies.

KEY WORDS: hypothalamic hamartoma, third ventricle, epilepsy, surgery, gelastic seizures, corpus callosum

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Presented at the International Symposium on Hypothalamic Hamartoma and Epilepsy, Montreal Neurological Institute, Montreal, Canada, November 29th 2001.

Resections for hypothalamic hamartoma (HH) in patients with intractable epilepsy have generally employed trans-sylvian or subfrontal approaches to the lesion, with a significant number of patients having residual lesion, ongoing seizures or neurovascular complications (see review and table in Rosenfeld *et al.*, 2001) [1]. A recently published surgical series of 13 patients collected from four centres highlights the potential complications associated with these approaches [2]. Minimally invasive endoscopic, stereotactic [3] and radiosurgical [4, 5] approaches to HH offer promise, but all experience is limited. HH that cause epilepsy usually have a significant third ventricular component [6], with attachment to the mammillary body on one or both sides. This intrahypothalamic component may be important in the generation of seizures. We previously reported our early experience with resection of HH via a transcallosal interforaminal approach to the third ventricle [1, 7], the advantages of this approach being the clear view gained of the HH in the third ventricle, the ability to resect the HH using anatomical landmarks, minimal cortical disruption accessing the HH, and avoidance of important neurovascular structures which lie beneath the HH. To date, the neurosurgeon author (JVR) has performed transcallosal resection of HH in 44 children and adults with refractory gelastic epilepsy. Preoperative and postoperative findings are presented here for the series of 29 consecutive patients investigated and operated at the Royal Children's Hospital, Melbourne until June 2002, for whom minimum postoperative follow-up is 12 months.

Patients and methods

Twenty-nine patients with HH and intractable epilepsy underwent surgery at the Children's Epilepsy Program of the Royal Children's Hospital, Melbourne; 24 patients underwent surgery at approximately monthly intervals over the last two years. Patient referrals were from the United States of America in 12, Australia in 7, United Kingdom in 5, Hong Kong in 3, Germany in 1 and Tanzania in 1.

Preoperative and postoperative evaluations

All patients underwent detailed preoperative and postoperative clinical, EEG, imaging, psychological, endocrine and ophthalmological assessments. The protocol for endocrine investigation is presented elsewhere in this issue (Freeman *et al.*). Neurological examinations and ophthalmological assessments were performed preoperatively and postoperatively in all cases, with visual perimetry performed in cooperative patients.

Conventional volumetric MRI acquisitions at 1.5 T were obtained in all patients, with thin, reformatted slices. High-resolution, high-contrast, T2-weighted images in coronal, axial and sagittal planes were also obtained and were found to be most helpful in showing the HH, the

normal hypothalamic grey nuclei, and the heavily myelinated fornices, mammillary bodies and mammillothalamic tracts. MRI was repeated postoperatively using an identical protocol and the percentage of HH resected was estimated.

Detailed seizure histories were obtained and past medical notes and EEG reports were reviewed where available. Prolonged video-EEG monitoring was performed in 28/29 patients. Ictal or early postictal SPECT with Tc^{99m}-HMPAO was combined with video-EEG monitoring in 24 patients, and interictal SPECT was performed in 19. EEG was repeated after surgery and any change in spike-wave activity between preoperative and postoperative EEGs was calculated.

Neuropsychological assessment of cognitive abilities, behavioural problems and the impact of epilepsy was performed in all cases. The test batteries administered depended on each patient's age and developmental abilities. Where possible, detailed assessment of memory was undertaken. Neuropsychological assessment was repeated postoperatively.

Due to the large proportion of patients referred from overseas, preoperative testing was generally performed in the week prior to surgery. Similarly, postoperative neurological, EEG, MRI, endocrine, visual and neuropsychological evaluations were performed between 2-3 weeks following surgery in most patients. Long-term follow-up of seizure outcome, medication usage, development, behaviour, weight and biochemical testing was in person for the seven Australian patients and via correspondence with the patient's family and treating doctors in the 22 overseas patients. Analysis of seizure outcome with respect to patient and HH features was done using Fisher's exact test for categorical data and the Mann-Whitney test for continuous age data.

Patient characteristics

The mean age at transcallosal surgery was 10 years (range 4-23 years). Prior treatment failures included anticonvulsant drugs in 29 patients, a ketogenic diet in six and vagal nerve stimulation in four. One patient had undergone prior temporal lobectomy and one a frontotemporal corticectomy. Eight patients had undergone prior HH surgery including resection via a subfrontal or trans-sylvian approach in seven, radiofrequency thermocoagulation in three and stereotactic radiosurgery in one.

The HH varied in size on MRI from a small spheroid approximately 7mm in diameter to a large irregular lesion with diameters of 28 × 34 × 42 mm in three planes. The proportion of the lesion lying above the normal level of the floor of the third ventricle (intraventricular component) varied from 100% to less than 10%. The smallest lesions encountered were attached to the hypothalamus above the mammillary body on one side and lay entirely within the third ventricle. Most HH extended into the interpedun-

cular cistern, and in four cases extended to the pontine level. The mammillary region of the hypothalamus was involved in all patients. Unilateral or predominantly unilateral attachment of the HH was seen in 6 and 12 cases respectively.

Gelastic seizures were present in all patients at some stage. In addition, 27 patients had complex partial seizures, 20 had tonic seizures (11 with drop attacks) and six had tonic-clonic seizures. Average seizure frequency was 10 per day. All but one patient had an abnormal interictal EEG; most patients had frequent generalised or lateralised spike-wave discharges which increased markedly in sleep. Nineteen patients had the electroclinical phenotype of symptomatic generalised epilepsy at the time of surgery, defined as the presence of (i) tonic seizures or epileptic spasms, and (ii) abundant spike-wave activity, with or without electrodecrements. Ictal EEG patterns were variable with many patients having either no ictal EEG change (typically in gelastic seizures), widespread low voltage generalised fast activity (typically in tonic seizures) or lateralised or asymmetric frontotemporal fast and/or spike-wave patterns (typically in partial seizures). Temporal or frontal 'pseudolocalisation' was seen in many patients. Confirmation of HH seizure origin with specific modalities was not a requirement for surgery; rather, an electroclinical picture consistent with HH seizure origin, with or without subsequent seizure spread, and absence of a cortical lesion or incongruous electroclinical picture, were the bases for proceeding with surgery. A variable

degree of HH ictal hyperperfusion was present in many patients (data analysis in progress) (*figure 1*); in those patients early in our series, HH hyperperfusion was a major impetus to for resection of the lesion. Intracranial EEG monitoring was not employed in any of our patients.

Thirteen patients had central precocious puberty, 21 had intellectual disability and 18 had behavioural problems including outbursts of rage and aggression.

Operative technique

A small frontoparietal craniotomy was performed and the right hemisphere was gently retracted. Using the operating microscope, a 1.5-2.0 cm opening was made in the anterior portion of the body of the corpus callosum just behind the genu (*figure 2a*), protecting the pericallosal vessels. The third ventricle was entered between the leaves of the septum pellucidum and the most anterior segment of the fornices, where the fornices part along the anterior border of the foramina of Monro to pass inferiorly as the columns (*figure 2b*). The trajectory of this anterior approach was generally towards the centre or posterior part of the HH in the third ventricle, corresponding to the tuberal and mammillary regions of the hypothalamus.

The HH was usually seen in the third ventricle as a smooth mass, often with a cleft between it and the ventricular wall. Large HH sometimes filled and distorted the third ventricle, obscuring the lateral walls. The HH was removed using an ultrasonic aspirator, using the walls of the third

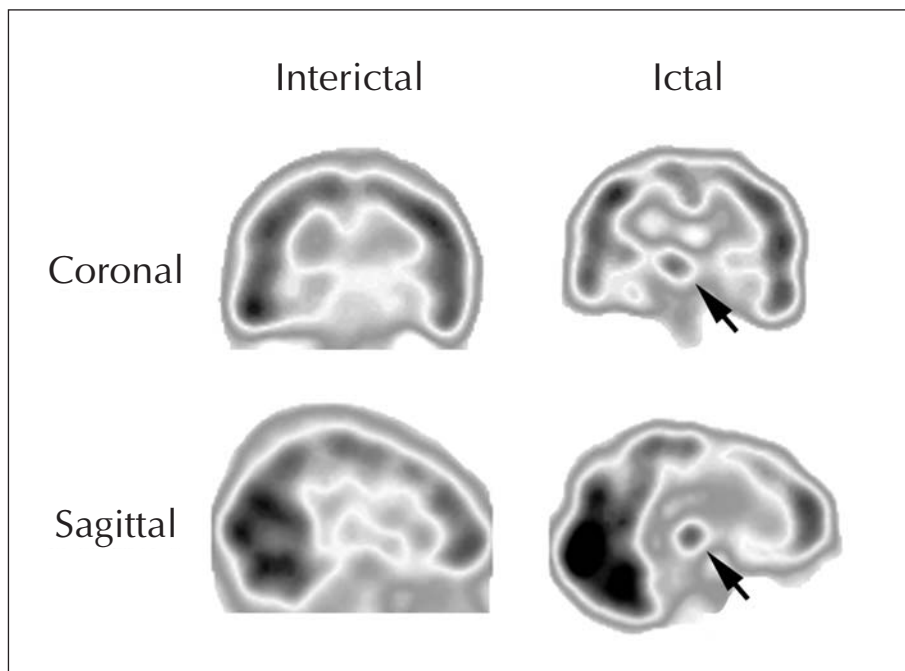


Figure 1. Interictal and ictal Tc^{99m} HMPAO SPECT scans in a 12 year-old boy with intractable epilepsy and a small intraventricular HH of approximately 6 mm diameter, attached to the hypothalamus on the right side. In the ictal study, a radiopharmaceutical was injected during a gelastic seizure, 40 seconds from seizure onset and showed focal hyperperfusion within the HH (black arrow).

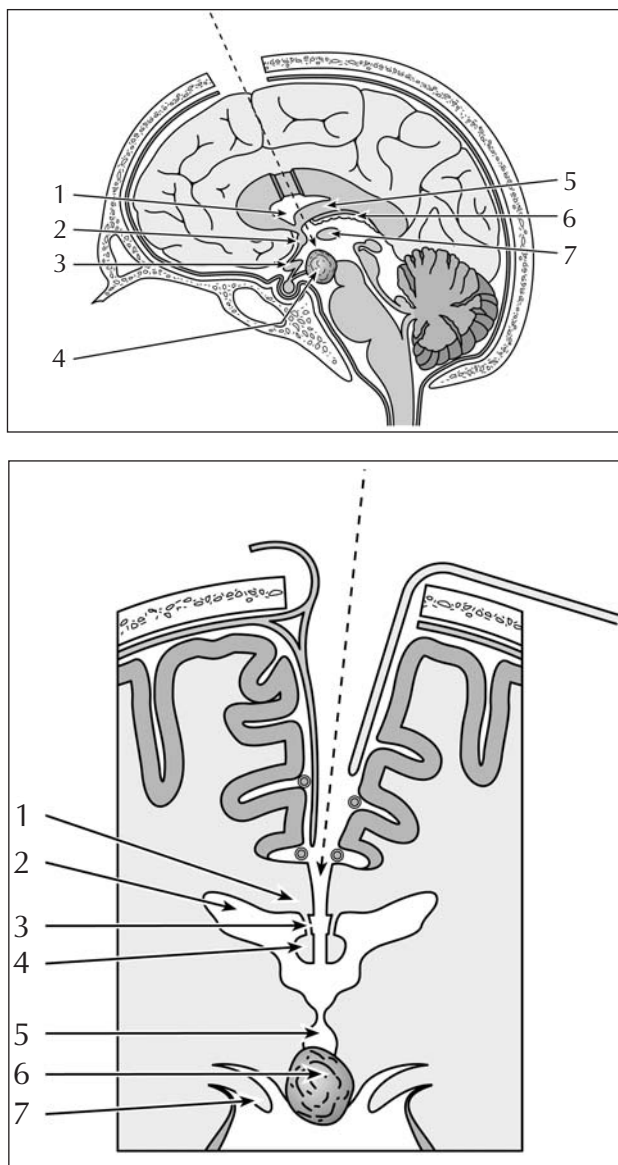


Figure 2. a) Illustration (midline sagittal view) showing trajectory of the anterior transcallosal approach as determined by frameless stereotaxy, small frontal craniotomy and small anterior callosal incision. Labeled are the (1) septum pellucidum, (2) anterior commissure, (3) optic chiasm, (4) hypothalamic hamartoma, (5) fornix, (6) choroid plexus of the third ventricle, and (7) intermediate mass. b) Illustration (coronal view) showing parafalcine interhemispheric approach, minimal retraction of the right frontal lobe and midline incision in the corpus callosum, between pericallosal vessels. Labeled are (1) corpus callosum, (2) cavity of the lateral ventricle, (3) septum pellucidum, (4) fornix, (5) cavity of the third ventricle, (6) hypothalamic hamartoma and (7) optic tract.

ventricle as the lateral limit of the resection and the translucent pial floor of the third ventricle as the inferior limit of the resection, at least in the mid and anterior portions. Posteriorly, the HH was invariably attached to the mammillary bodies and attempts were made to pre-

serve these and their connections. The HH was usually rubbery and gliotic in consistency, making it relatively distinguishable from the surrounding soft normal cerebral tissue around it in most cases.

Results

Comparison of preoperative and postoperative MRI scans revealed that greater than 95% resection of the HH was achieved in 18/29 patients (figure 3), with 100% resection seemingly achieved in 12 patients. Between 75% and 95% resection was achieved in seven patients, four of whom had complete or near-complete disconnection of the residual hamartoma lying anteriorly, laterally or inferiorly. Less than 50% of the HH was resected in four patients. Incomplete resection was likely if the HH was attached anteriorly to the pituitary stalk and optic chiasm, if the HH extended inferiorly in the interpeduncular recess to the level of the pons, if the HH had a broad base on the lateral hypothalamus, or if the HH was so large that it filled the third ventricle and distorted the lateral and posterior margins of the third ventricle. Histopathology was consistent with a hamartoma in all cases.

A small, unilateral, anterior thalamic-capsular infarct occurred in two patients, both of whom had diathermy in the resection bed to arrest bleeding from perforating vessels. Subtle hemiparesis and an incomplete unilateral third nerve paresis resolved completely by the end of the first postoperative week in one of these two patients. Mild-moderate hemiparesis resolved completely over several months in the other patient. No postoperative visual defects occurred in any patient.

Early short-term memory disturbance, manifesting typically by repeated questioning, was noted in 14 patients. In most cases this resolved over several days or weeks, but in four cases, memory impairment persisted to a significant degree; one patient had previously undergone a left temporal lobectomy with resultant severe verbal memory impairment, and another patient had previously undergone resections and radiofrequency ablations of the hamartoma, complicated by middle cerebral artery territory stroke. From parent reports, there was the impression of improving memory function over several months in these affected patients.

Postoperative follow-up for the 29 patients ranged from one to nearly six years (mean 30 months, range 12-70 months). Seizure evolution and postoperative outcome are shown schematically in figure 4. Seizures occurred in the first postoperative week in 16 (59%) patients. These tended to lack the gelastic component of the preoperative seizures, occurred primarily from sleep, were predominantly tonic in nature, and in most patients decreased in frequency or ceased over subsequent months. In terms of current seizure status, 15 patients are seizure-free (patients 4, 5, 9, 11-18, 20, 21, 26, 29), seven have seizures at

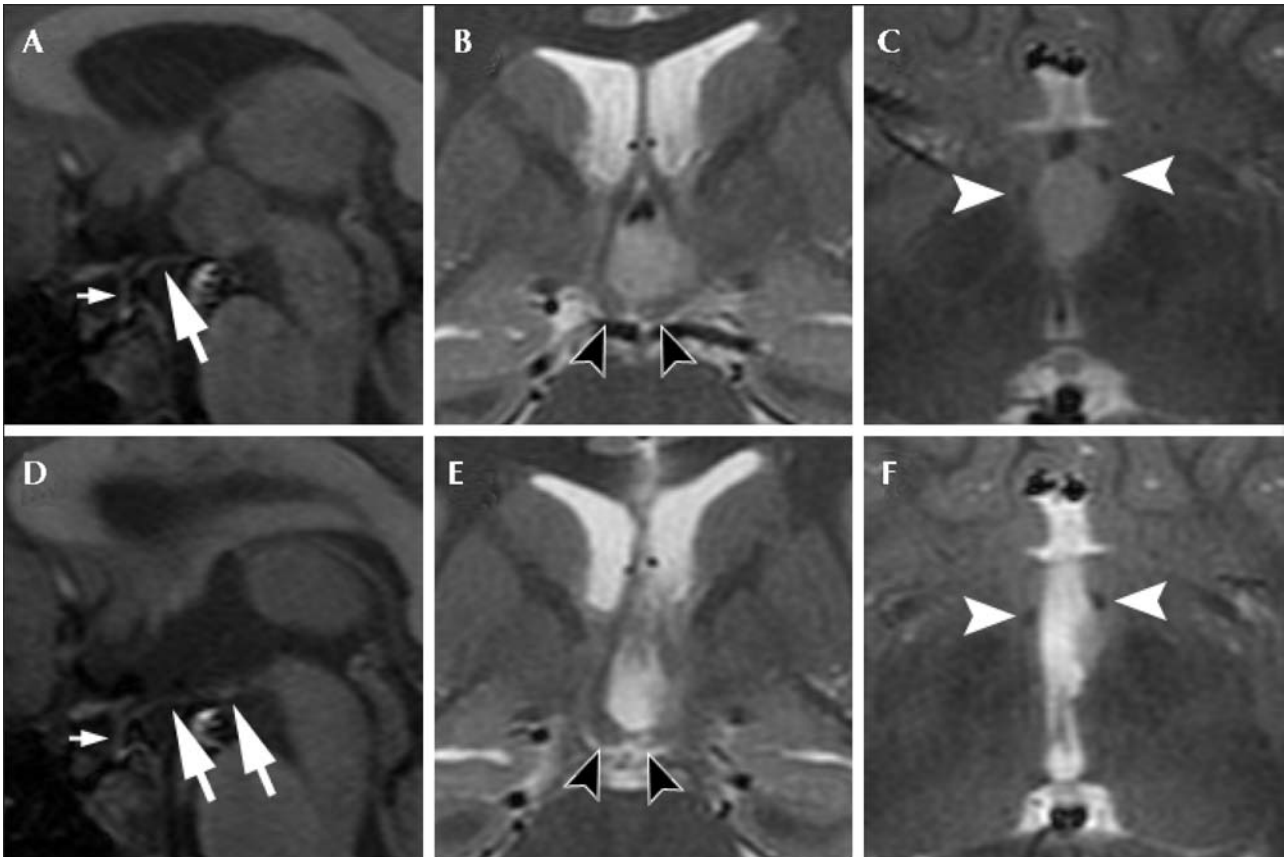


Figure 3. MRI scans of an 11 year old boy with intractable gelastic and tonic seizures. Magnified views of his hypothalamic region and 10 mm diameter intraventricular HH are shown before (top row) and after (bottom row) surgery in T1-weighted sagittal (A and D), T2-weighted coronal (B and E) and T2-weighted axial (C and F) sequences. Greater than 95% removal of the HH was achieved following anterior transcallosal resection; a small remnant of HH remains on the left hypothalamus (E and F). The arrows highlight various normal structures preserved during surgery: floor of third ventricle (pair of large white arrows, A and D), pituitary stalk (small white arrow, A and D), mammillary bodies (black arrow heads, B and E), and fornices (white arrow heads, C and F).

> 90% reduced frequency (patients 1, 2, 3, 8, 25, 28 and patient 22 at time of death), three have seizures at 55–80% reduced frequency (patients 7, 23, 27), one has seizures at 40% reduced frequency (patient 10), and three have seizures at the same frequency as prior to surgery (patients 6, 19, 24). Six of the seizure-free patients had seizures in the early postoperative period that subsequently remitted. Persistent seizures for many patients were auras or brief gelastic events in which the parents noted a sudden behavioural change, maybe with a smile, but with no laughter or impairment of consciousness. Only four patients had seizure recurrence after a year or more of seizure-freedom, these being infrequent auras or mild partial seizures at a much reduced frequency in three (patients 1, 2, 3), and seizures of the same severity and magnitude as preoperatively in one (patient 6). No patient had worsening of seizure frequency or severity following surgery. Most patients are on reduced medication and nine seizure-free patients are on no antiepileptic medication. Seizure-freedom following surgery was not associated with (i) preoperative clinical findings such as intellectual

disability ($P = 1.0$), behaviour disorder ($P = 0.6$) or precocious puberty ($P = 0.6$), (ii) HH characteristics such as maximum diameter ($P = 0.5$) or proportion of HH being intraventricular in location ($P = 0.4$), (iii) the proportion of HH resected, analysed for both > 95% ($P = 0.6$) and 100% ($P = 0.6$) resection, or (iv) patient age at seizure onset ($P = 0.1$) or age at surgery ($P = 0.2$). Similarly, seizure-freedom was not associated with the absence of symptomatic generalised epilepsy ($P = 0.2$), the age-at-onset of tonic seizures specifically ($P = 0.8$) or the duration of tonic seizures prior to surgery ($P = 0.3$).

Paralleling the resolution of seizures in these patients was a gradual reduction in slow spike-wave activity on interictal scalp EEG, most notable in the SGE patient group with abundant spike-waves. Twelve of the 19 patients with SGE were the subject of a detailed perioperative EEG analysis reported elsewhere [8]. The mean percentage of EEG containing spike-wave activity in these 12 patients decreased from 17% to 4% in awake EEGs and from 48% to 19% in asleep EEGs, with spike wave being abolished in the awake EEG in seven patients.

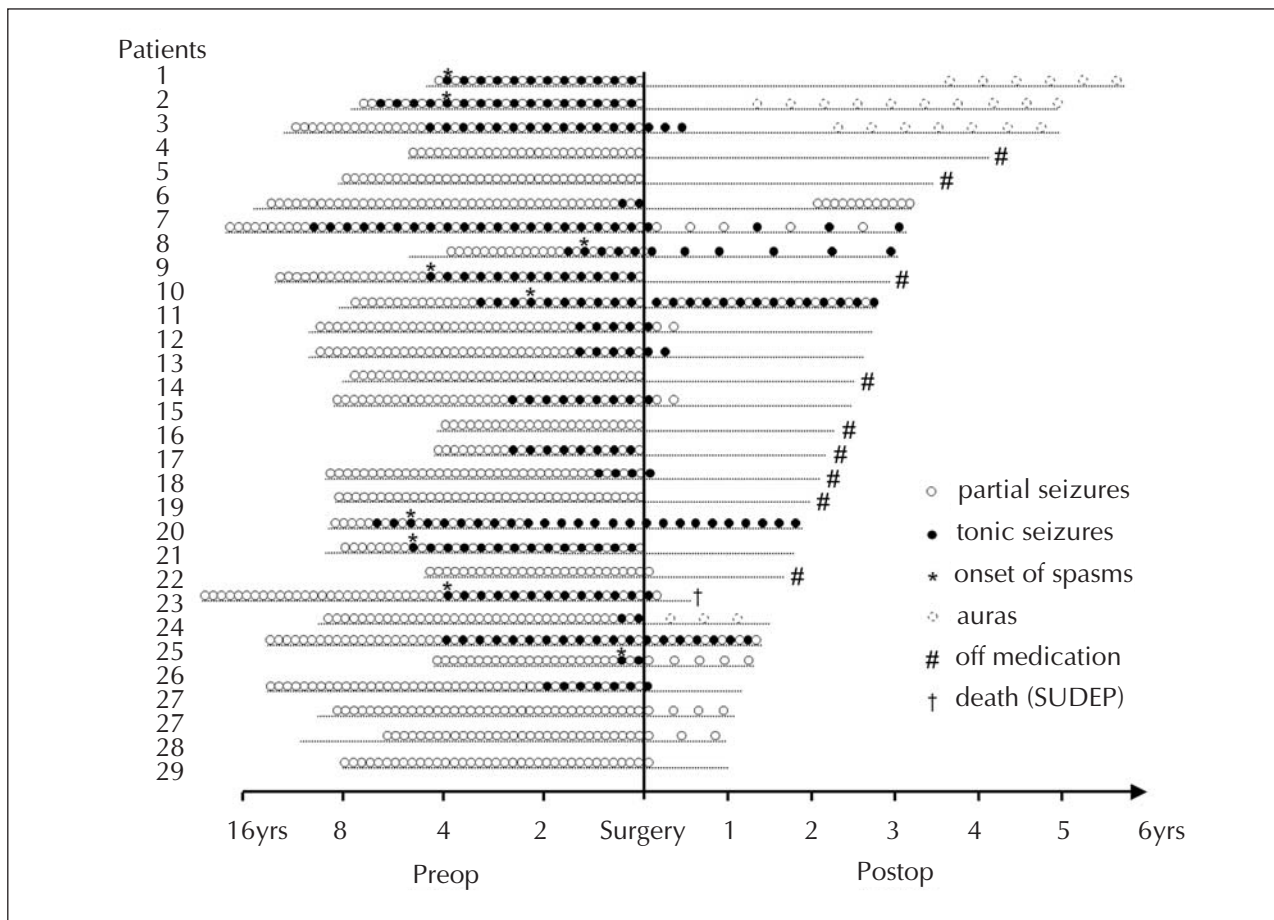


Figure 4. Schematic representation of seizure evolution over time leading up to transcallosal surgery, and then the change in seizures following surgery for 29 patients, with minimum 12 months follow-up (mean 30 months). The time scale is non-linear on the left side of surgery, showing the age of the patient and duration of epilepsy, but is linear on the right of surgery, representing the duration of postoperative follow-up. Seizures are plotted along a dotted line representing each patient's life. Seizures are separated into two groups to highlight patients with and without SGE. Partial seizures include gelastic, simple partial and complex partial seizures. Tonic seizures include typical tonic seizures, drop attacks and epileptic spasms; an asterisk denotes the onset of epileptic spasms in affected patients. Auras are brief events where patients or parents noted the start of a gelastic or partial seizure without impairment of consciousness and without laughter. Patients off antiepileptic medication are highlighted.

There were early postoperative improvements in behaviour, attentiveness and speech output observed in many children. Three autistic, non-verbal children began to speak soon after surgery. These early postoperative behavioural improvements were maintained, with loss of aggression and cessation of rage episodes in all patients with favourable seizure outcomes and in one of the patients with no seizure improvement. Mood disturbance occurred in three seizure-free patients and required antidepressant medication. Two non-seizure-free patients developed psychotic symptoms during periods of postoperative seizure fluctuation, both of whom had prior psychiatric disturbances.

One patient, the oldest in the series, died suddenly and unexpectedly in his sleep seven months after surgery. Seizures were reduced by greater than 95% and an initial

postoperative exacerbation of a preoperative psychosis had resolved. No cause of death was found at postmortem, and therefore death was regarded as SUDEP.

Discussion

A variety of surgical approaches exist to treat intractable epilepsy associated with HH. Resection of HH from classical subfrontal and trans-sylvian routes, with or without cortical resection for improved access, have been associated with significant risks of stroke, cranial nerve palsy, endocrinopathy and residual lesion with postoperative seizures [1, 2]. These approaches provide limited access to the HH, especially the intrahypothalamic component, when the third ventricle is entered from beneath. Greater

access to the intrahypothalamic component may be obtained by entering the third ventricle via a trans-lamina terminalis approach, various transcallosal approaches, a transcortical trans-foraminal (Monro) approach, or a supratentorial or infratentorial approach from behind [9, 10]. Although the trans-lamina terminalis approach is favoured by many neurosurgeons, there is retraction of both frontal lobes to gain access and potential for injury to the olfactory nerves, optic chiasm and the anterior cerebral arteries; furthermore, there is restricted access to the inferior and posterior margins of the HH in the third ventricle, rendering it more difficult to obtain resection or disconnection of the HH attached to the mammillary bodies.

Three transcallosal approaches to the third ventricle are described: (i) the midline interforaminal approach [12], (ii) the transforaminal approach through the lateral ventricle and the foramen of Monro [10, 12, 13], and (iii) the transchoroidal or subchoroidal approach traversing the choroidal fissure, the velum interpositum or tela choroidea between the fornix and the thalamus [12, 14, 15]. In our modified, transcallosal, interforaminal approach, the third ventricle is entered more anterior to that described by Apuzzo and Amar [11]. We favour this transcallosal approach to HH with an intraventricular attachment, even when there is a large interpeduncular component, because of the better view of the HH in the third ventricle, the ability to perform microsurgical resection from within the lesion, the surgical landmarks provided by the lateral and inferior margins of the third ventricle, and the separation from critical neurovascular structures beneath the HH.

Small subcortical stroke with transient hemiparesis occurred in two of our 29 patients, most probably as a result of diathermy of perforating vessels between the HH and the floor of the third ventricle. Permanent cranial nerve injury did not occur in our surgical series. Postoperative endocrine disturbance was minimal, with transient hypernatraemia, mild thyroxine deficiency and weight gain being the only endocrine consequences of surgery in some patients (see Freeman *et al.* in this issue). This minimal endocrinological and neurological morbidity contrasts with that reported when subfrontal or trans-sylvian operative approaches to HH are employed [1, 2], most likely due to the limited traction of the frontal lobe, the separation from major neurovascular structures and the pituitary stalk, the resection being performed with gentle aspiration from entirely within the lesion, and the avoidance of diathermy where possible.

Short-term memory disturbance due to septal, forniceal or mammillary body injury is the major disincentive to third ventricular surgery. Transient short-term memory impairment was reported by Apuzzo and Amar in 30% of patients in their series who underwent classical interforaminal resection of third ventricular lesions; in 75% of

patients the memory disturbance resolved in the week after surgery and by 3 months, all had returned to preoperative status [11]. In our transcallosal approach, the fornices are retracted laterally to some degree, more on the side of entry (right side) than the other side, but probably less overall than with a more posterior approach. We were usually able to preserve the mammillary bodies and their connections (as seen on postoperative T2-weighted MRI scans in three planes), even if the HH distorted these structures. This is because the fornices are displaced around the edge of the lesion and the mammillary bodies are usually displaced to the inferiolateral edge of the HH. When the HH was attached unilaterally, surgical trauma was presumably limited to memory structures on the one side and may not have been clinically apparent. Short-term memory disturbance may have been undetected in non-verbal or intellectually disabled patients in our series, or alternatively, may have recovered promptly or been adapted in young children, due to cerebral plasticity.

Our postoperative seizure results, with 76% of patients being seizure-free or having a 90% or greater reduction in seizures (mean follow-up 2.5 years), are comparable to those reported with anterior temporal lobectomy in patients with mesial temporal lobe epilepsy [16]. The results are somewhat surprising, considering the long-standing and sometimes progressive nature of the patients' epilepsies and associated neurobehavioural problems. Interestingly, no patient or lesion characteristics were predictive of seizure freedom following surgery. This suggests that young patients of any age, with HH of any size and intraventricular location, who have intractable epilepsy of any duration and severity may become free of seizures with transcallosal surgery.

Most striking was the neurological improvement in patients with SGE, in whom the majority showed marked improvement or remission of gelastic, partial and tonic seizures, reduction in spike-wave activity or EEG normalisation, acceleration in development, and improvement in behaviour. The evolution of SGE from gelastic seizures is well described [17], and has been proposed as a model for both progressive epilepsy [18] and pervasive developmental disorders of childhood [19]. In our series, the decrease in interictal spike-wave activity was not immediate following resection of the HH, and the resolution of tonic seizures took up to six months in some cases. Delayed seizure remission is described following other surgical approaches to HH [20], and spike wave discharges on the scalp EEG of patients with HH have been shown to not necessarily correlate with discharges originating in the HH [8, 21]. We have proposed that the slow spike-wave activity and tonic seizures that develop over time in some patients with HH, are extralesional phenomena related to secondary epileptogenesis [8]. The electroclinical remission in our SGE patients is similar to that described by Morrell for patients he classified as having the intermediate form of secondary epileptogenesis [22]. One potential

anatomical conduit for the propagation of seizures from the HH and the remote generation of generalised spike-wave is the mammillothalamic tract, whose fibers ascend to the anterior thalamic nucleus and then project to the anterior cingulate gyrus [23].

Our surgical series of HH patients is the largest reported, with all patients operated upon with a standardised perioperative protocol and a single operative approach over a relatively short period at a single institution. We have shown that it is feasible and safe to resect HH via a transcallosal interforaminal approach to the third ventricle with microsurgical removal and stereotactic guidance. We believe that the remarkable seizure improvement is related to removal or disconnection of the intraventricular, intrahypothalamic component of the HH. The low frequency and benign nature of complications are most likely due to being able to adequately visualise and operate entirely within the HH, limit the resection to the margins of the third ventricular walls and pial floor, minimise traction on the frontal lobes and fornices, and avoid diathermy during resection. Based on published surgical series, we believe that the transcallosal approach is superior to conventional trans-sylvian and subfrontal approaches to HH, with respect to completeness of resection, seizure outcome and complications. The challenges ahead for clinicians managing these complex cases are (i) comparing long-term efficacy and morbidity of HH resections with radiosurgical approaches, (ii) establishing criteria for patient selection and timing of surgery, (iii) refining surgical techniques to further minimise risks to memory and endocrine function, and (iv) understanding why apparently complete HH resection does not render some patients seizure-free.

Acknowledgements

The authors thank Ms Catherine Bailey (EEG Technologist), Ms Elizabeth Grimmer (Nurse Specialist), Mr Michael Kean (MR Technologist), Ms Jacqueline Wrennall (Clinical Neuropsychologist), Dr Margaret Zacharin and her endocrinologist colleagues, the neuroscience nursing staff, and the anaesthetic and operating suite staff for their important contributions to the management of this patient group. We are also grateful to the patients, their families and the Hypothalamic Hamartoma Uncontrolled Gelastic Seizures (HHUGS; <http://www.geocities.com/hhugs2001>) support group, who had faith and trust in our epilepsy program and assisted us with collection of accurate clinical information and follow-up; their efforts have definitely advanced knowledge and led to treatment advances in this rare and frequently devastating condition. □

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