Disconnecting Surgical Treatment of Hypothalamic Hamartoma in Children and Adults With Refractory Epilepsy and Proposal of a New Classification

Olivier DELALANDE and Martine FOHLEN

Unité de neurochirurgie pédiatrique, Fondation Ophtalmologique A. de Rothschild, Paris, France

Abstract

A series of 17 patients aged from 9 months to 32 years with refractory epilepsy due to hypothalamic hamartoma were treated by total removal (one case) and disconnection (16 cases) between 1997 and 2002. The mean age at seizure onset was 16 months. Sixteen patients had gelastic seizures, 14 had partial seizures and three had generalized tonic-clonic seizures. The mean seizure frequency was 21 per day. Four patients had borderline intelligence quotient and the others were mentally retarded. Five patients presented with precocious puberty, one with acromegaly, and four suffered from obesity. Brain magnetic resonance imaging, performed at least twice in each patient, showed the hamartoma as a stable homogeneous interpeduncular mass implanted either on the mammillary tubercle or on the wall of the third ventricle with variable extension to the bottom. Ictal single photon emission computed tomography, performed in four patients, showed hyperperfusion within the hamartoma in two patients. Twenty-five operations were performed in the 17 patients. The first patient underwent total removal of the hamartoma, whereas the following 16 patients underwent disconnection through open surgery (14 procedures) and/or endoscopy (9 procedures). Eight patients became seizure-free, one patient had only brief gelastic seizures, and eight patients were dramatically improved with a mean follow up of 18.6 months (8 days to 43 months). Surgery was safe in all but two patients: the first patient had transient hemiplegia and the third cranial nerve paresis, and the other developed hemiplegia due to ischemia of the middle cerebral artery territory. The quality of life, and behavior and school performance were greatly improved in most patients. Our series illustrates the feasibility and relative safety of disconnection surgery for hypothalamic hamartomas with seizure relief in 53% of patients and dramatic improvement in the others. Surgical observations led us to propose a new anatomical classification according to the anatomical relationship between the hamartoma and the adjacent hypothalamus and third ventricle. Endoscopic disconnection seems to be a very safe way to treat hamartomas in intraventricular locations.

Key words: hypothalamic hamartoma, gelastic epilepsy, disconnecting surgery, children

Introduction

Hypothalamic hamartomas are rare congenital

lesions consisting of mixed neurons and glial cells⁹⁾ that usually take the form of nodules located on the wall or the floor of the third ventricle or attached to

Hypothalamic hamartoma associated with intractable epilepsy is a major problem when surgical management is discussed. Professor Olivier Delalande is Chief Neurosurgeon of the Department of Pediatric Neurosurgery, Fondation Ophtalmologique Adolf de Rothschild, in Paris, France. In recent international symposia, he has reported a series of hypothalamic hamartoma in children and adults with refractory epilepsy, managed with various surgical techniques according to his new classification of hypothalamic hamartomas. With the permission of Professor Akira Yamaura, Chief Editor of the *Neurologia medico-chirurgica*, this stimulating paper has appeared in this issue. The strategies of his surgery using surgical excision, surgical disconnection or endoscopic disconnection are challenging but safe. His surgical outcomes are that 8 patients are seizure free, one patient has only brief gelastic seizures and 8 patients are dramatically improved. I hope that the authors will have the opportunity to again examine the outcomes in their series several years from now.

Tatsuya TANAKA, M.D., D.M.Sc.,
President of the 30th Annual Meeting of the Japan Society for Pediatric Neurosurgery.

the tuber cinereum or mammillary bodies. Hypothalamic hamartomas are often associated with an epileptic syndrome which usually begins in early childhood with gelastic seizures and later continues as generalized epileptic encephalopathy characterized by other types of seizures (partial and generalized) and associated with cognitive decline and behavioral disorders.^{4,17} The epilepsy is frequently refractory to antiepileptic drugs. Depth electrode recordings have demonstrated that gelastic seizures arise within the hamartoma,^{1,3,5,7,11,13} so resection of the hamartoma seems to be the most appropriate treatment.

Recently, various therapeutic approaches for epilepsy have been attempted with encouraging results, including gamma knife surgery,^{2,18,22} radio-frequency thermocoagulation,⁷ and chronic electrical stimulation of the hamartoma and microsurgery using different routes.^{14,15,20,23} Most previous studies have included single cases or series, some of precocious puberty only, others with epilepsy only or both.^{10,12}

We recently reported disconnection of hamartoma of the fourth ventricle which resulted in total relief of seizures in two patients.⁶ In the present study, we performed disconnection of the hamartoma using either open cranial surgery or endoscopic surgery guided with a frameless stereotactic robot in a series of 17 children and adolescents referred for intractable epilepsy due to hypothalamic hamartoma, and propose a classification for hamartoma to aid in the selection of the surgical treatment.

Materials and Methods

I. Patients

Seventeen patients, 12 males and five females aged at surgery from 9 months to 32 years (mean 13.8 years), were treated for refractory epilepsy associated with hypothalamic hamartoma between January 1997 and January 2002 in our department (Table 1). Prior to surgery, the patients underwent neurological examination and neuropsychological assessment, routine electroencephalography (EEG) and video-EEG monitoring, magnetic resonance (MR) imaging, and endocrinological investigations.

The onset of the epilepsy ranged from the neonatal period to 24 months (mean 16 months) and the age at diagnosis of hypothalamic hamartoma ranged from 1 month to 10 years (mean 3 years). The seizure types were classified as follows: infantile spasms (1/17 patients), gelastic seizures (16/17), dacrystic seizures (2/17), partial seizures (14/17), tonic seizures (8/17), atonic seizures (2/17), and generalized tonic clonic seizures (3/17). Eight of 17 patients experienced

three seizure types, seven patients had two seizure types, and two patients had four seizure types. The seizure frequency ranged from six seizures per hour to four seizures weekly (mean 21 seizures daily).

Neurological examination showed no motor deficit in any patient. One patient had congenital deafness and was classified as Pallister-Hall syndrome (Case 4). Neuropsychological examination performed at the time of the operation showed border line intelligence quotient (IQ) in four patients, mild mental deficiency (IQ 40–80) in six, and severe mental deficiency (IQ < 40) in five. The two infants had developmental quotients of 64 and 60. Five children among the most mentally impaired patients (Cases 1, 4, 8, and 10) had behavioral problems that encompassed hyperkinesia, aggressiveness, and psychotic features. One patient had frontal syndrome (Case 16) and another had anxiety disorders (Case 7). The other patients presented with no major behavioral disorders.

Endocrinological disorders were observed in nine patients; four had polyphagia associated with obesity, five had precocious puberty, and one had gigantism associated with acromegaly and hypothyroidism. None of our patients had any visual impairment.

MR imaging was performed at least twice in each patient. All hamartomas were stable lesions appearing as iso-intense on T₁-weighted images without enhancement by contrast medium and iso- or hyper-intense on T₂-weighted images. All hamartomas were sessile with variable attachment to the hypothalamus and great variation in size. Ictal single photon emission computed tomography was performed in four patients, showing hyperperfusion within the lesion in two patients and no abnormalities in the other two patients.

II. Classification of hamartomas and surgical procedures

Twenty-five operations were performed in the 17 patients, as eight patients required reoperations (Table 2).

Case 1 underwent complete resection of the lesion through a pterional route. Postoperatively, he became seizure-free (Engel class I) but developed partially regressive right hemiplegia and left third cranial nerve paresis. These complications were unforeseen considering the operative conditions. Clinical signs and postoperative MR imaging suggested a vascular complication. Therefore, to avoid further complications, we decided to perform disconnection associated with variable resection in the subsequent patients.

Various surgical procedures have been evolved for

Table 1 Clinical summary of cases

Case No.	Sex	Age at onset	Type: No. of seizures	Endocrinology	Neuropsychology and behavior	MR imaging*
1	M	neonatal	GS: 4/day; TS: 3–4/wk; CPS: variable	no dysfunction	severe mental deficiency, hyperkinesia, aggressiveness	III
2	M	1 yr	GS: 3/day; TS: 4/day	precocious puberty (7 mos)	mild mental deficiency, normal social behavior	III
3	M	3 mos	GS: 4–5/day; TS: 0–2/day; CPS: 4–5/day	no dysfunction	severe mental deficiency, hyperkinesia	I
4	M	1 yr	GS and DS: 5–50/day	no dysfunction	severe mental deficiency, hyperkinesia	I
5	F	2 yrs	GS: 1/day; AS and CPS: 2–3/wk	precocious puberty (2 yrs)	mild mental deficiency (IQ 44), normal social behavior	III
6	M	6 yrs	GS, DS, and CPS: 1–4/day; several GTCS	obesity and hypercholesterolemia	border line IQ, normal social behavior	I
7	M	1 yr	GS and CPS: 1–8/day; TS: 3/wk	precocious puberty (9 yrs)	mild mental deficiency (IQ 62), normal social behavior	III
8	F	1.5 yrs	CPS and AS: 3–5/day	no dysfunction	severe mental deficiency, autistic behavior	III
9	M	5 mos	GS, TS, and CPS: 20–40/day	precocious puberty (4.5 yrs), obesity	mild mental deficiency	I
10	M	1 mo	GS and CPS: 4–5/day; GTCS: 2/day	obesity	severe mental deficiency, hyperkinesia, aggressiveness	III
11	F	6 wks	GS and CPS: every 10 min	precocious puberty	developmental delay (DQ 60)	IV
12	M	14 mos	GS, TS, and CPS	hypothyroidism, acromegaly	mild mental deficiency (IQ 49), normal social behavior	III
13	M	2 yrs	GS and CPS: 4/wk	no dysfunction	border line IQ, normal social behavior	III
14	M	neonatal	IS and GS	no dysfunction	developmental delay (DQ 64)	II
15	M	2 yrs	GS, TS, and CPS: 0–4/day	obesity	border line IQ, normal social behavior	I
16	F	7 yrs	GS, GTCS, TS, and CPS: 3–4/wk	no dysfunction	mild mental deficiency, social problems	II
17	F	neonatal	GS and CPS	no dysfunction	border line IQ, normal social behavior	III

*Type of personal classification. AS: absence seizure, CPS: complex partial seizure, DQ: developmental quotient, DS: dacrystic seizure, GS: gelastic seizure, GTCS: generalized tonic-clonic seizure, IQ: intelligence quotient, IS: infantile spasm, TS: tonic seizure.

the anatomical conditions of hamartomas. We have developed a classification for hamartomas based on the plane of insertion on the hypothalamus to help choose the best surgical route (Fig. 1).

Hamartoma Type I has a horizontal implantation plane and may be lateralized on one side; the microsurgical route should be pterional leading to complete disconnection (Cases 3, 4, 6, 9, and 15).

Hamartoma Type II has a vertical insertion plane and intraventricular location; the surgical procedure consists of disconnection of the intraventricular component of the hamartoma using an endoscop-

ic route with a frameless stereotactic robot and the endoscopic resection can be repeated if required (Cases 14 and 16).

Hamartoma Type III is a combination of Types I and II; we recommend a two-step procedure: the first step consists of disconnection of the intraventricular part of the hamartoma using an endoscopic route and the second step consists of disconnection through a pterional route (Cases 1, 2, 5, 7, 8, 10, 12, 13, and 17).

Hamartoma Type IV includes all giant hamartomas for which no specific surgical procedures can

Table 2 Surgical procedures

Case No.	No. of operations	Surgical procedure	Age at surgery	Outcome	Follow up*	Behavior and social outcome	Endocrinological outcome	Duration of follow up**
1	1	complete resection	12 yrs	relief of all types of seizure	I	improved	no change	5 yrs 4 mos
2	2	conventional disconnection	8 yrs 10 yrs	relief of TS, GS ameliorated (90%)	II	improved	hypothyroidism and growth hormone deficiency	22 mos
3	1	endoscopic disconnection conventional disconnection	19 yrs	relief of GS and CPS, TS ameliorated (90%)	III	no change	hyperphagia and weight gain	4 yrs 3 mos
4	1	conventional disconnection	3.5 yrs	relief of all types of seizure	I	improved	precocious puberty onset 4 mos after operation	4 yrs 2 mos
5	1	conventional disconnection	18 yrs	relief of GS, AS and CPS ameliorated (80%)	III	no change	normal	4 yrs
6	1	conventional disconnection	15 yrs	relief of all types of seizure	I	improved with school performance in progress	no change	3 yrs 10 mos
7	2	conventional disconnection	16 yrs 18 yrs	relief of TS, GS and CPS ameliorated (80%)	III	IQ improved by 16 points	normal	4 yrs 3 mos
8	2	endoscopic disconnection conventional disconnection	7 yrs	CPS and AS ameliorated (90%)	III	no major change, still autistic	normal	24 mos
9	1	endoscopic disconnection conventional disconnection	8 yrs 10 yrs	relief of TS, CPS and GS ameliorated (90%)	III	improved	transient diabetes insipidus	3 yrs 5 mos
10	2	conventional disconnection	7 yrs	relief of all types of seizure	I	improved with speech in progress	no change	6 mos
11	1	endoscopic disconnection conventional disconnection	9 yrs 14 mos	GS and CPS ameliorated (>90%)	III	improved	panhypopituitarism	30 mos
12	2	conventional disconnection	16.5 yrs	relief of all types of seizure	I	improved	normal	25 mos
13	2	endoscopic disconnection conventional disconnection	18.5 yrs 16.5 yrs	relief of all types of seizure	I	improved	transient diabetes insipidus	21 mos
14	1	endoscopic disconnection	17 yrs 9 mos	relief of all types of seizure	I	DQ improved by 11 points	normal	14.5 mos
15	1	conventional disconnection	17.5 yrs	relief of all types of seizure	I	improved	no change	15 mos
16	2	endoscopic disconnection	31 yrs	reduction of all types of seizure	III	no change	no change	2 mos
17	2	endoscopic disconnection conventional disconnection endoscopic disconnection	32 yrs 4 yrs	insufficient	III	no change	no change	1 mo

*Engel class. **Since the last operation. AS: absence seizure, CPS: complex partial seizure, DQ: developmental quotient, GS: gelastic seizure, IQ: intellectual quotient, TS: tonic seizure.

be recommended (Case 11).

According to our classification, 14 patients underwent disconnection through a pterional route and nine patients (7 reinterventions and 2 primary interventions) underwent endoscopic surgery with the aid of a frameless stereotactic robot.

Postoperative complications consisted of meningitis (Case 3), hemiplegia due to ischemia of the middle cerebral artery territory (Case 5), ischemic lesion of the internal part of the frontal lobe (Case 13), and transient diabetes insipidus (Cases 9 and 13). None of the patients who underwent endoscopic dis-

nection suffered any postoperative complications and all were discharged only 3 days after the operation.

Results

I. Effect on seizures

The completeness of disconnection of the hamartoma is difficult to assess during the operation because of the lack of clear-cut borders between the lesion and the hypothalamus, so the effect on the epilepsy remains the only indicator of adequate dis-

Fig. 1 Anatomical classification. A: Type I, B: Type II, C: Type III, D: Type IV.

connection.

The first patient (Case 1) became seizure-free (follow up 5 years) and demonstrated dramatic improvement of behavior and language performance. Antiepileptic drugs were withdrawn 2 years after the operation.

The 14 patients who underwent open surgery had the following outcomes: three patients became seizure-free (Engel class I), and 11 showed a dramatic reduction of frequency > 80% of all types of seizures (Engel class III) with total disappearance of tonic and generalized tonic-clonic seizures in five patients. Seven of these 11 patients underwent an additional endoscopic disconnection with a follow up of 3 months to 4 years (mean 21 months). Three patients became seizure-free (Cases 10, 12, and 13), one had only gelastic seizures (Case 2), and three showed reduced seizure frequency (Cases 7, 8, and 17).

Two patients underwent only endoscopic disconnection; one became seizure-free (Case 14) and the other was Engel class III (Case 16) after the first operation and was recently reoperated with no marked improvement (follow up 6 months).

The outcomes for all surgical approaches with a mean follow up of 18.6 months (8 days to 43 months) were seizure-free in eight patients, only brief gelastic seizures (Engel class II) in one patient, and dramatically improved (Engel class III) in eight patients.

II. Other results

Behavior, as evaluated by the families of the patient and their physicians, and school performance were improved in Engel class I to III patients. No patient experienced any cognitive aggravation. One patient obtained a driving license, two patients are learning manual skills, and one patient (class II) has an improved IQ of 16 points 15 months following surgery.

Two patients had definitive postoperative neurological deficits. Endocrinological follow-up examination showed hyperphagia with weight gain in one patient, hypothyroidism in one, and no change in the others.

III. Histopathology

Histological examination of the tumor samples found neuronal tissue made of scattered neurons and glial cells. The cellularity was sometimes increased or normal. The glial cells were mainly microglia. The neuronal cells were sometimes ganglionic neurons and in some cases the neurons had a degenerative aspect characterized by loss of basophilia of the cytoplasm.

Discussion

I. Surgical approaches and techniques

Various operative routes for the surgical treatment of hypothalamic hamartomas have achieved various degrees of reduction of epilepsy.^{8,14,15,20,23} In all cases the goal of the treatment was the removal of the entire lesion since it is commonly agreed that the hamartoma is the trigger of the epilepsy^{3,5,7,8,11,13,21} and so the resection of hypothalamic hamartoma must be as complete as possible to achieve good seizure remission.¹⁶

The present study suggests that complete removal of the hamartoma can be replaced by disconnection, using either open surgery or endoscopy, since the hamartoma is a stable lesion and entire anatomical removal is not necessary to treat the epilepsy. Such a surgical method was first applied to epilepsy in the form of hemispherotomy²⁴ instead of hemispherectomy with similar results upon the outcome of seizures, with corresponding reduction in the operative risks and postoperative complications. More recently, we performed disconnection in two children with hamartoma of the fourth ventricle associated with facial hemispasms, with excellent outcome regarding the seizures.⁶ Moreover, the endoscopic approach allows disconnection of the intraventricular part of the hamartoma and is very well tolerated by the patients; in case of failure or insufficient results, the procedure can be performed again. The problem is to define accurately the borders of the disconnection since there are no clear-cut limits between the hamartoma and the neighboring normal brain tissue.

Recently, a series of five children were treated with transcallosal resection.²⁰ Three became seizure-free and two were improved. The only postoperative complications were endocrinological such as hyperphagia and transient diabetes insipidus. Our endoscopic route is very similar to this transcallosal approach but it seems to us that the transcallosal approach may be inadequate for cases in which the implantation of the hamartoma spreads horizontally below the hypothalamus (Delalande's Type I), for which we recommend open surgery with a pterional route.

Another challenge is to attempt to classify the hamartomas in order to define the best surgical procedure. In 1994, Valdueza et al.²³ proposed a classification for hamartomas into four types (Ia, Ib, IIa, and IIb) based on the anatomical and clinical data from 42 patients (personal cases and literature selection). Types Ia and Ib were defined as small pedunculated hamartomas attached to the tuber cinereum. Clinically the patients are either asymptomatic or have precocious puberty. Surgical removal

is indicated only in the rare event of visual disturbance or to avoid long-term luteinizing hormone-releasing hormone analogue medication. Type II tumors consist of hamartomas larger than 1.5 cm with a sessile attachment to the floor of the third ventricle and the mammillary bodies without (IIa) or with (IIb) distortion of the third ventricle. Clinically the patients suffer from epilepsy associated with memory disturbances (IIa) and mental and behavior abnormalities (IIb). The surgical approach to type II hamartomas is recommended because of the failure to control the seizures with medication, but the operative route was not discussed.

Our 17 cases are consistent with Valdueza's type II as all had a sessile attachment to the hypothalamus with or without distortion of the wall of the third ventricle associated with epilepsy. We have proposed another classification of these cases into four types based on the anatomy only, as we could detect no differences in the severity of epilepsy or behavioral problems correlated with the size or implantation of the hypothalamic hamartomas. We suggest that the major feature in the planning of the optimum surgical management is the plane of attachment (horizontal, vertical, or both) of the lesion to the hypothalamus.

II. Surgery or radiosurgery

Radiosurgery appears to be an alternative treatment for hypothalamic hamartoma with epilepsy. In 2000, Regis et al.¹⁸ reported a series of eight patients with sessile hypothalamic hamartoma and drug-resistant epilepsy who were treated with gamma knife surgery (GKS). Four of these patients were cured or greatly improved and the remaining four patients exhibited marked improvement after a median latency in seizure cessation of 9 months. No side effects were reported within a median follow up of 28 months. The main argument advocated for radiosurgical treatment rather than microsurgery is the surgical risk of the resection of the hamartoma.

In our series, the first patient who underwent total resection of a large pediculate hamartoma experienced postoperative complications such as oculomotor nerve paresis and hemiplegia. Therefore, in the following consecutive patients, we decided to perform disconnection of the lesion rather than resection. With this approach, complications are infrequent, the effects on epilepsy quickly appear, and endoscopic disconnection can be repeated in the case of failure. In addition, patients do not suffer the long-term complications reported in patients undergoing GKS for mesial temporal lobe epilepsy.¹⁹ Moreover, large implanted as well as

small intraventricular lesions can be cured by disconnection, whereas Regis et al.¹⁸⁾ suggested that only small hypothalamic hamartomas located inside the third ventricle or in the floor are good candidates for GKS.

III. Other treatment approaches

In 1999, Fukuda et al.⁷⁾ reported a single patient with hypothalamic hamartoma treated by stereotactic radiofrequency thermocoagulation in the course of an exploration with a depth electrode implanted within the lesion, associated with subdural grids. Two gelastic seizures were recorded, originating from the hamartoma. The stimulation electrode was replaced by a coagulation electrode to treat the patient. Gelastic seizures ceased postoperatively whereas tonic seizures disappeared 4 months later. This patient is now seizure-free with a follow up of 14 months. To the best of our knowledge, this is the only case treated in that way and this technique seems to be suitable for Valdeuza's Type II hamartomas.

IV. Conclusion

Our series illustrates the feasibility and acceptable morbidity of disconnective surgery for treating hypothalamic hamartomas. This surgery is likely to become safer as technical procedures evolve. The safest method is stereotactic endoscopy indicated for cases with endo- or periventricular hypothalamic insertion. Since the prognosis of epilepsy linked to hypothalamic hamartomas is currently poor, surgical treatment has to be performed early, as soon as the epilepsy is identified as drug resistant, to prevent behavioral disorders and delayed development in children. Parents and patients must be aware that it is often necessary to operate twice or even more in cases of failure to control seizures and that disconnection performed under open surgery can be followed by endoscopic disconnection in cases of persistent seizures.

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Address reprint requests to: O. Delalande, M.D., Unité de neurochirurgie pédiatrique, Fondation Ophtalmologique A. de Rothschild, 25 rue Manin, 75019 Paris, France.
e-mail: odelalande@fo-rothschild.fr.