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Hypothalamic hamartoma with refractory epilepsy: surgical procedures and results in 18 patients

Martine Fohlen[1], Arielle Lellouch[2], Olivier Delalande[1]

1. Unité de Neurochirurgie Pédiatrique, Fondation Ophtalmologique A. de Rothschild
2. Service d'Anatomo-pathologie, Hôpital Necker-Enfants Malades, Paris, France

ABSTRACT – Aim: to study the surgical procedures and results on seizures, in 18 patients with refractory epilepsy due to hypothalamic hamartoma.

Patients and methods: Eighteen patients aged from 9 months to 32 years underwent surgery between 1997 and 2002. The mean age at seizure onset was 15.5 months. Seventeen patients had gelastic seizures, 14 had partial seizures, two had infantile spasms, 10 had tonic or atonic seizures and three had generalized seizures. The mean seizure frequency was 21 per day. Four patients had borderline intellectual disability and the others were mentally retarded. Five patients had precocious puberty, one had acromegaly and four suffered from obesity. Brain MRI, performed at least twice in each patient showed the hamartoma as a stable, homogeneous interpeduncular mass implanted either on the mammilary tubercle or on the wall of the third ventricle, with variable extension to the bottom. Ictal SPECT, performed in four patients, showed hyperperfusion within the hamartoma in two.

Surgical procedure: twenty-six operations were performed in 18 patients. The first patient underwent a total removal of the hamartoma, whereas the following patients underwent a disconnection, either through open surgery (14 patients) or endoscopy (10 patients).

Results: regarding the seizure outcome with a mean follow up of three years four months (one year to 4.5 years), nine patients are seizure-free, one patient has only brief gelastic seizures and eight are dramatically improved. Surgery was uncomplicated in all but two patients: one had transitory hemiplegia and paresis of the third cranial nerve, the other presented with hemiplegia due to ischemia of the middle cerebral artery territory. The quality of life, behavior and school performance were greatly improved in most of the patients.

Conclusion: our series illustrates the feasibility and relative safety of disconnecting surgery of hypothalamic hamartomas, with seizure relief in 50% and a dramatic improvement in the others. Endoscopic disconnection seems to be a very safe way to treat the intra-ventricular part of hamartomas.

KEY WORDS: hypothalamic hamartoma, gelastic epilepsy, disconnecting surgery, children

Correspondence:
Martine Fohlen,
Unité de Neurochirurgie Pédiatrique, Fondation Ophtalmologique A. de Rothschild
25, rue Manin 75019 Paris, France.
Tel: 33-1-48-03-68-17
Fax: 33-1-48-03-65 52
E-mail: mfohlen@fo-rothschild.fr

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Hypothalamic hamartomas (HH) are rare congenital lesions consisting of mixed neurons and glial cells [1] that usually take the form of nodules located on the wall or on the floor of the third ventricle, or attached to the tuber cinereum or mammillary bodies.

The epilepsy syndrome associated with HH usually begins in early childhood with gelastic seizures, and continues, later on, with a generalized epileptic encephalopathy characterized by other types of seizures (partial and generalized), and associated with cognitive decline and behavioral disorders [2, 3]. The epilepsy is frequently refractory to antiepileptic drugs. Since some authors [4-9] have demonstrated with depth electrode recordings that gelastic seizures arise within the hamartoma, the resection of the hamartoma seems to be an appropriate treatment. Recently, various therapeutic approaches have been attempted with encouraging results on seizure control: gamma knife surgery [10-12], radiofrequency thermocoagulation [8], chronic electrical stimulation of the hamartoma, and microsurgery using different routes [13-16]. We recently described in 17 patients, a technical procedure consisting of a disconnection of the hamartoma using either an open cranial surgery approach or endoscopic surgery guided with a frameless stereotactic robot, and we proposed a new anatomical classification [17]. In the present paper we report, with a longer follow-up, the surgical procedure and results on seizures of, 18 patients, mainly children, referred for intractable epilepsy due to HH.

Patients and methods

Eighteen patients (13 males and five females) with refractory epilepsy due to HH underwent surgery between January 1997 and July 2002 (see *table 1*). Their age at surgery ranged from 9 months to 32 years (*m* = 12.3 years). Prior to surgery, the patients underwent neurological examination and neuropsychological assessment, routine EEG and video-EEG monitoring, MRI and endocrinological investigations. The onset of the epilepsy ranged from the first days of life to 24 months (mean: 15.5 months), and the age at diagnosis of HH ranged from one month to 10 years (mean: three years).

The seizure types were classified as follows: infantile spasms (2/18), gelastic seizures (17/18), dacrystic seizures (2/18), partial seizures (14/18), tonic seizures (8/18), atonic seizures (2/18) generalized tonic clonic (3/18) seizures. Eight of the 18 patients experienced three seizure types, eight patients had two seizure types and two had four seizure types. The seizure frequency ranged from six seizures per hour to four seizures weekly, with an average of 21 seizures daily.

Neurological examination showed no motor deficit in any patient. One patient had congenital deafness, and he was classified as Pallister-Hall syndrome (case No 4). Neuropsychological examination performed at the time of the operation showed a borderline intellectual quotient in four patients, a mild mental deficiency (IQ between 40 and 80) in seven and severe mental deficiency (IQ below 40) in five. One infant had a developmental quotient of 64 and the other, 60.

Six children among the most mentally impaired (cases 1, 3, 4, 8, 10, 18) had behavioral problems that encompassed hyperactivity, aggressiveness and psychotic features. One patient had a frontal syndrome (case 16), and another had an anxiety disorder (case 7). The other patients did not have major behavioral disorders.

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

MRI was performed at least twice in each patient. The results showed the hamartoma as a non-enhancing, stable lesion with an iso-intense signal on T1-weighted images and an iso- or hyper-intense signal on T2-weighted images. In all cases, the implantation of the hamartoma was sessile with variable attachment to the hypothalamus and there was a great variety of size of the lesion.

Ictal SPECT was performed in four patients: in two cases it showed a hyperperfusion within the lesion and in the remaining two, it appeared to be non-contributive.

Surgical procedure

Twenty-six operations were performed in 18 patients: eight patients have been operated on twice.

The first patient underwent complete resection of the lesion, performed through a pterional route. Postoperatively, he became seizure-free (Engel class 1) but developed a right hemiplegia that partially improved, and a left 3rd nerve palsy. Such a complication was unforeseen, and a post-operative MRI scan suggested a vascular complication. In order to avoid similar complications, we decided to proceed, in the following patients, with a disconnection associated with variable resection.

Over time, surgical procedures evolved with the purpose of making surgery suitable for the anatomical conditions of the hamartoma. In order to decide the best surgical route, we developed a classification with four types, based on the plane of insertion of the hamartoma upon the hypothalamus (see *figure 1*).

In type I, the implantation plane is horizontal and may be lateralized on one side; the microsurgical route will be pterional leading to a complete disconnection. (cases 3, 4, 6, 9, 15).

In type II, the insertion plane is vertical and intraventricular and the surgical procedure consists of a disconnection of the intraventricular component of the hamartoma using an endoscopic route with a frameless stereotactic robot (cases 14, 16); the endoscopic resection can be repeated in the case of an insufficient result.

In type III hamartomas, we suggest proceeding in 2 steps: the first step consists of the disconnection of the intraventricular part of the hamartoma using an endoscopic route, and the second step consists of a disconnection through a pterional route (cases 1, 2, 5, 7, 8, 10, 12, 13, 17, 18).

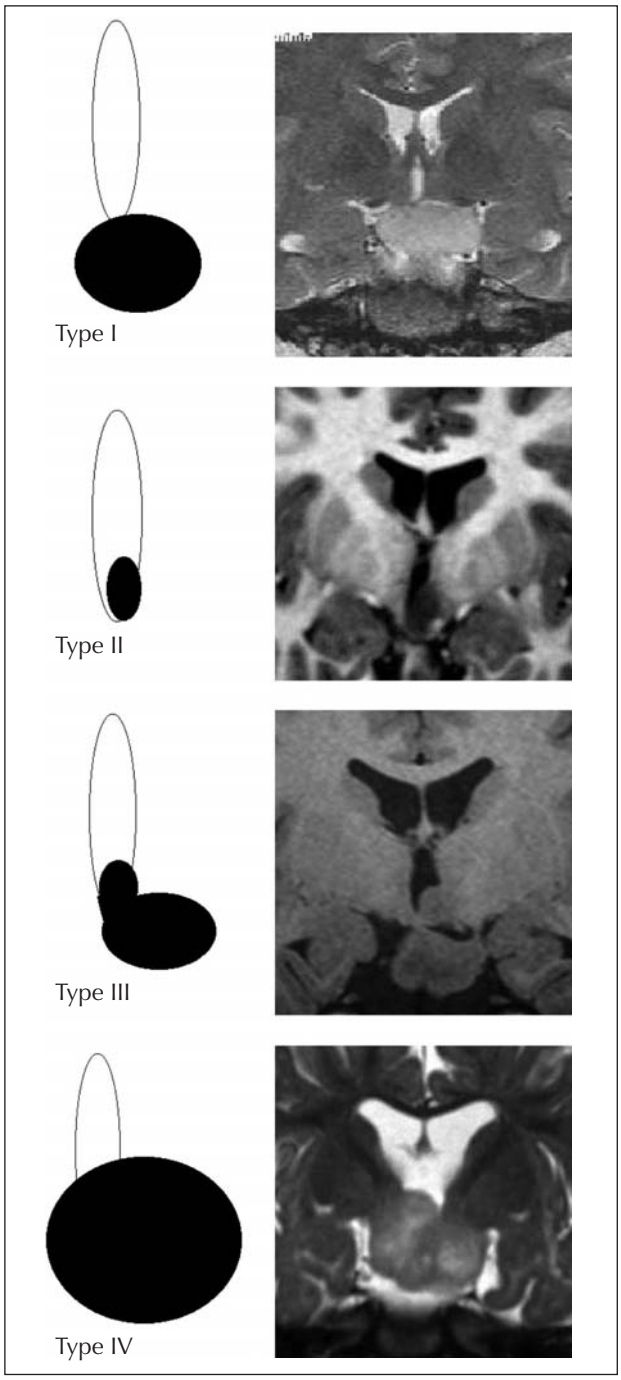

Figure 1.

Type IV defines giant hamartomas and for these there are no specific surgical rules Case 11).

According to this classification, 14 patients have had a disconnection through a pterional route and ten patients (seven reinterventions and three primary interventions) underwent endoscopic surgery with the aid of the frameless stereotactic robot.

Post-operative 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, 13).

None of the patients who underwent endoscopic disconnection have had any post-operative complications, and all of them were discharged from hospital three days after surgery.

Results

Seizure results

The first patient became seizure-free (follow-up: six years) and demonstrated a dramatic improvement in behavior and language performance. Antiepileptic drugs were withdrawn two years after the operation.

The fourteen patients who underwent open surgery had the following results: three patients became seizure-free (Engel class 1), 11 had a dramatic reduction in seizure frequency > 80% (Engel class 3) of all types of seizures, 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 15 months to five years (mean: 27 months). Three patients became seizure-free (cases 10, 12, 13), one had only gelastic seizures remaining (case 2) and three showed reduced seizure frequency (case 7, 8, 17).

Among the three patients who underwent endoscopic disconnection only, two are seizure-free (case 14 and 18), and the other one is Engel class 3 (case 16) after the first operation and has been recently re-operated upon with no marked improvement (follow-up: 18 months).

In summary, considering all of the surgical approaches, nine (50%) patients are seizure-free, 1 patient (5%) has only brief gelastic seizures (Engel class 2), and eight (44%) are dramatically improved (Engel class 3).

Other results

Behaviour, as evaluated by the families of the patients and the physicians, as well as school performances are improved in Class 1 to Class 3 patients. No patient experienced any cognitive deterioration. One patient obtained his driving license, two patients are learning manual work and one patient (Class 2) has an IQ improved by 16 points, 15 months following surgery.

Two patients have definitive post-operative neurological deficits.

Endocrinological follow-up shows hyperphasia with weight gain in one patient, panhypopituitarism in another, and association of hypothyroidism, human growth hormon deficiency in the third with no change in the others.

Table 1. Clinical data of hypothalamic hamartomas.

Pt/DOB	Sex	Age at sz's onset	Type/number of seizure	Endocrinology	Neuropsychology and behavior	MRI (Personal classification)	Nb of operations
1 04/01/85	M	Neonatal	GS: 4/d, TS: 3-4/w, CPS: variable	no dysfunction	severe mental deficiency, hyperkinesia, aggressiveness	type III	1
2 20/11/89	M	1 y	GS: 3/d, TS: 4/d	precocious puberty (7 m)	mild mental deficiency, normal social behavior	type III	2
3 05/08/79	M	3 m	GS: 4-5/d, TS 0-2/d, CPS: 4-5/d	no dysfunction	severe mental deficiency, hyperkinesia	type I	1
4 08/09/94	M	12 m	GS, DS: 5-50/d	no dysfunction	severe mental deficiency, hyperkinesia	type I	1
5 28/08/79	F	2 y	GS: 1/d, AS & CPS: 2-3/w	precocious puberty (2 y)	mild mental deficiency (IQ 44), normal social behavior	type III	1
6 28/08/83	M	6 y	GS, DS, CPS: 1-4/d, several GTCS	obesity and hypercho-lesterolemia	borderline IQ, normal social behavior	type I	1
7 18/03/82	M	1 y	GS, CPS: 1-8/d TS: 3/w	precocious puberty (9 y)	mild mental deficiency (IQ 62), normal social behavior	type III	2
8 21/02/92	F	18 m	CPS, AS: 3-5/d	no dysfunction	severe mental deficiency, autistic behavior	type III	2
9 27/10/88	M	5 m	GS, TS, CPS: 20-40/d	precocious puberty (4, 5 y), obesity	mild mental deficiency	type I	1
10 19/12/92	M	1 m	GS, CPS: 4-5/d GTCS: 2/d,	obesity	severe mental deficiency, hyperkinesia, aggressiveness	type III	2
11 09/09/98	F	6 w	GS and CPS: every 10 mn	precocious puberty	developmental delay (DQ 60)	type IV	1
12 01/12/82	M	14 m	GS, TS, CPS	hypothyroidy, acromegaly	mild mental deficiency (IQ 49), normal social behavior	type III	2
13 16/07/83	M	2 y	GS, CPS: 4/w	no dysfunction	borderline IQ, normal social behavior	type III	2
14 15/06/00	M	neonatal	IS, GS	no dysfunction	developmental delay (DQ 64)	type II	1
15 30/07/83	M	2 y	GS, TS, CPS: 0-4/d	obesity	borderline IQ, normal social behavior	type I	1
16 27/06/69	F	7 y	GS, GTCS, TS, CPS: 3-4/w	no dysfunction	mild mental deficiency, social problems	type II	2
17 15/01/98	F	Neonatal	GS, CPS	no dysfunction	borderline IQ, normal social behavior	type III	2

Abbreviations: **M** = male; **F** = female; **y** = year; **m** = month; **Sz** = seizure; **GS** = gelastic seizure; **TS** = tonic seizure; **CPS** = complex partial seizure; **DS** = dacrystic seizure; **AS** = absence seizure; **GTCS** = generalized tonic-clonic seizure; **/d** = per day; **w** = per week; **IQ** = intellectual quotient; **DQ** = developmental quotient; **DOB** = date of birth.

Table 2. Hypothalamic hamartomas: surgical procedure outcome.

Pt	Surgical procedure	Age at surgery (Years)	Outcome of the Sz	Follow-up (Engel class)	Behavior and social outcome	Endocrinological outcome	Duration of follow-up (since the last operation)
1	complete resection	12.00	relief of all types of seizure	1	improved	no change	5 y 4 m
2	conventional disconnection endoscopic disconnection	8 10	relief of TS, GS ameliorated (90%)	2	improved	panhypopituitarism	22 m
3	conventional disconnection	19	relief of GS and CPS, TS ameliorated (90%)	3	no change	hyperphagia and weight gain	4 y 3 m
4	conventional disconnection	3.5	relief of all types of seizure	1	improved	precocious puberty onset 4 m after operation	4 y 2 m
5	conventional disconnection	18	relief of GS, AS and GSP ameliorated (80%)	3	no change	normal	4 y
6	conventional disconnection	15	relief of all types of seizure	1	improved school performance in progress	no change	3 y 10 m
7	conventional disconnection endoscopic disconnection	16 18	relief of TS, GS and CPS ameliorated (80%)	3	IQ improved by 16 points	normal	4 y 3 m
8	conventional disconnection endoscopic disconnection	7 8	CPS and AS ameliorated 90%	3	no major change, still autistic	normal	24 m
9	conventional disconnection	10	relief of TS, CPS and GS ameliorated 90%	3	improved	transient post-operative diabetis insipidus	3 y 5 m
10	conventional disconnection endoscopic disconnection	7 9	relief of all types of seizure	1	improved speech in progress	no change	6 m
11	conventional disconnection	14 months	GS and CPS ameliorated > 90%	3	improved	panhypopituitarism	30 m
12	conventional disconnection endoscopic disconnection	16.5 18.5	relief of all types of seizure	1	improved	normal	25 m
13	conventional disconnection endoscopic disconnection	1.5 17	relief of all of seizure	1	improved	transient post-operative diabetes insipidus	21 m
14	endoscopic disconnection	9 months	relief of all types of seizure	1	developmental quotient improved by 11 points	normal	14.5 m
15	conventional disconnection	17.5	relief of all types of seizure	1	improved	no change	15 m
16	endoscopic disconnection endoscopic disconnection	31 32	reduction of all types of seizures	4	no change	no change	2 m
17	conventional disconnection endoscopic disconnection	4	insufficient	3	no change	no change	1 m

Histopathology

Histologically, the sample removed consisted of neuronal tissue made of scattered neurons and glial cells. The cellularity was sometimes increased (cases 14, 15, 16) or normal (case 17). The glial cells were mainly microglia with a elongated cell aspect' (cases 14, 16). The neuronal cells were sometimes ganglionic neurons, and in three cases the neurons had degenerative features, characterized by the loss of basophilia of the cytoplasm and the disappearance of the Nissl bodies (cases 15, 17, 18); in two patients (cases 15, 17), axons were present in great numbers with numerous axonal bowls, which were disclosed by the neurofilament coloration. The combination of the lack of cytoplasmic basophilia, preservation of neuronal architecture, axonal bowls and macrophagic activity is consistent with a degenerative process.

Discussion

Since the first paper of Kammer in 1980 [18], several types of surgical approach and other techniques (radiosurgery, radiofrequency) have been reported for HH treatment. Most of these papers involve single cases or series, some with precocious puberty only, others with epilepsy only, or both [19].

Discussion of surgical approaches and techniques

Different operative routes for the surgical treatment of HH have been reported in the English literature [13-16, 20] with variable success on epilepsy outcome. In all of these cases, the goal of the treatment was the removal of the entire lesion since it is commonly believed that the hamartoma is the trigger of the epilepsy [4-8, 20, 21] and that, to achieve good seizure remission, the resection of HH must be as complete as possible [22].

Nevertheless, as previously reported [17] we believe that the complete removal of the hamartoma can be replaced by a disconnection, using either open surgery or endoscopy, since the hamartoma is a stable lesion and entire anatomical removal is not necessary for treating the epilepsy. Such a surgical strategy was first applied to epilepsy in the form of hemispherotomy [23] instead of hemispherectomy, with similar results upon the outcome of seizures, whereas operative risks and postoperative complications were lower. More recently, a disconnection was performed on two children with hamartoma of the fourth ventricle associated with facial hemispasms, with an excellent outcome regarding the seizures [24]. Moreover, the endoscopic approach allows a disconnection of the intraventricular part of the hamartoma and is very well tolerated by the patients; in case of failure or insufficient results, it can be performed again. The difficulty is to accurately define the borders of the disconnection since there are no clear-cut limits between the hamartoma and the neighboring normal brain tissue (also see Freeman, this issue), so, the outcome of the epilepsy remains the only evidence of a sufficient disconnection.

Recently, Rosenfeld *et al.* described a series of five children who underwent transcallosal resection [16]. Three of them are seizure-free and two are improved. The only postoperative complications were endocrinological, such as hyperphagia and transient diabetes insipidus (see Harvey *et al.*, this issue).

Our endoscopic route is very similar to this transcallosal approach but it seems to us that the transcallosal approach may be insufficient for cases in which the implantation of the hamartoma spreads horizontally below the hypothalamus (Delalande's type 1), and in the latter we recommend open surgery with a pterional route.

Discussion of operative *versus* radiosurgery gamma knife surgery treatment

Radiosurgery appears to be an alternative treatment of HH with epilepsy. In 2000, Regis *et al.* reported a series of eight patients with sessile HH and drug-resistant epilepsy treated with gamma knife surgery (GKS) [12]. Four of these patients were seizure-free or have greatly improved, and the remaining four patients exhibited marked improvement after a median latency in seizure cessation of nine months. No side effects were reported within a median follow-up of 28 months. The main argument advocated for the radiosurgical treatment rather than microsurgery is the surgical risk of the resection of the hamartoma (see also Regis, in this issue). Our first patient who underwent total resection of a large pediculate hamartoma had postoperative complications of oculo-motor palsy and hemiplegia. Therefore, in the following patients, we decided to perform disconnection of the lesion rather than resection. With such an approach, the complications are infrequent, the results as regards the epilepsy are apparent shortly after, and endoscopic disconnection can be repeated in case of failure. In addition, patients are protected from long term complications reported in GKS mesial temporal lobe epilepsy [25]. Moreover, large, implanted as well as small, intraventicular lesions can be treated by disconnection, whereas, only small HH located inside the third ventricle or in the floor are good candidates for GKS.

Other treatment approaches

In 1999, Fukuda reported a single patient with HH 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. In order to cure the patient, the electrode of stimulation was replaced by an electrode allowing coagulation. Gelastic seizures ceased thereafter, whereas tonic seizures disappeared four months later. This patient is now seizure-free with a follow-up of 14 months [8]. To the best

of our knowledge, he is the only patient treated in this way and this technique seems to be suitable for type II hamartomas of Valdueza's classification.

Conclusion

Our series illustrates the feasability and acceptable morbidity of disconnective surgery in hypothalamic hamartomas. This kind of surgery has become safer as technical procedures evolve. The safest method is stereotactic endoscopy which is appropriate for cases with endo- or periventricular hypothalamic insertion. Since the prognosis of epilepsy linked to HH is currently poor, surgical treatment has to be performed early, as soon as the epilepsy appears to be drug-resistant in order to prevent behavioral disorders and delayed development in children. □

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