Childs Nerv Syst (2005) 21: 817–824
DOI 10.1007/s00381-005-1205-6

SPECIAL ANNUAL ISSUE

A. Pierre-Kahn
C. Recassens
G. Pinto
C. Thalassinos
S. Chokron
J. C. Soubervielle
R. Brauner
M. Zerah
C. Sainte Rose

Social and psycho-intellectual outcome following radical removal of craniopharyngiomas in childhood

A prospective series

Received: 11 April 2005
Published online: 28 July 2005

A. Pierre-Kahn (✉) · M. Zerah · C. Sainte Rose
Department of Pediatric Neurosurgery,
Groupe hospitalier Necker Enfants Malades Paris,
149 rue de Sèvres,
75743 Paris, Cedex 15, France
e-mail: alain.kahn@nck.ap-hop-paris.fr

C. Recassens
CMPP, Saint Maure des Fossés, France

G. Pinto · C. Thalassinos · R. Brauner
Department of Endocrinology,
Groupe hospitalier Necker Enfants Malades, Paris, France

S. Chokron
Department of Neurology,
Fondation Ophtalmologique Rothschild, Paris, France

J. C. Soubervielle
Department of Medical Biology,
Groupe hospitalier Necker Enfants Malades, Paris, France

Abstract *Background:* A prospective study on childhood craniopharyngiomas (CPs) was conducted from 1994 to 1998 to appreciate the pre- and postoperative clinical, endocrine, mental, and intellectual status of the patients and to determine the incidence and severity of the postoperative hypothalamic syndrome.
Methods: The series included 14 consecutive CPs. Twelve were retrochiasmatic and intraventricular, and two were partly prechiasmatic and extraventricular. All were treated with the aim of "total" removal. The removal was "total" in nine cases but incomplete in the other five. Immediate postoperative follow-up was uncomplicated in all cases.
Conclusion: At 2-year follow-up, the two children with an extraventricular CP and a "total" tumor removal were intellectually normal, had no hypothalamic syndrome, and attended normal school with good results. The 12 others, although still intellectually normal, were more or less severely affected by a hypothalamic syndrome which altered their social insertion and caused academic failure. The authors conclude from this study that radical surgery should be reserved to extraventricular CPs only.

Keywords Craniopharyngioma · Surgery · Hypothalamic syndrome · Outcome

Introduction

Craniopharyngiomas (CPs) are one of the most frustrating tumors in pediatric neurosurgery. On the one hand, they are curable after total removal. On the other hand, total removal is often impossible and attempts at it may induce severe complications. Recent advances in preoperative imaging and new technical surgical refinements have lowered the risks of postoperative mortality to almost zero but have not substantially changed the level of postoperative morbidity. Some of the sequelae, of course, are not attributable to neurosurgeons: they are the irremediable consequences of the preoperative tumor growth and/or diagnostic delay. But this is not the case for many others. Among the latter, one of the worst is the hypothalamic syndrome, which simply hinders normal life and makes socialization and education impossible or severely altered. Curiously, the syndrome has not been described in adult

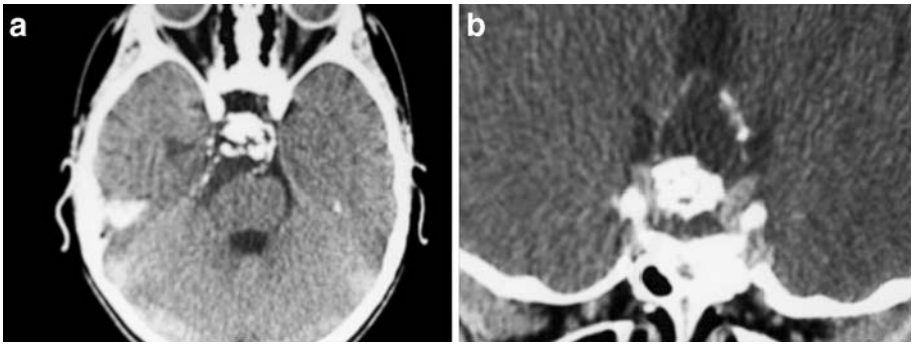

Fig. 1 Preoperative noninjected CT scan of the child showing large intra- and suprasellar calcifications typical of a CP on axial (**a**) and coronal (**b**) planes

series of CPs (as if it did not exist in adulthood) and only rarely in pediatric ones. This is astounding, knowing its potentially devastating social effects. The severity and the deepness of the parents' and children's distress that can result from this syndrome will be described through a case report from our series that illustrates most of the features of the syndrome. This is precisely the case that incited us to better appreciate the incidence of the syndrome after attempts at total removal of CPs. In 1994, a prospective series was begun for this purpose. All the children included in the study were pre- and postoperatively evaluated from clinical, endocrine, intellectual, psychological, academic, and social points of view.

Illustrative case

P.J.P. is a Caucasian boy born in March 1980 who grew up uneventfully until the age of seven when he began rapidly developing an evolving precocious puberty. He was referred to our outpatient clinic because of the radiological discovery [skull X-rays and computed tomography (CT) scan] of an intra- and suprasellar cystic and calcified mass typical of a CP (Fig. 1). The extension of the tumor was better defined on magnetic resonance imaging (MRI), which showed a large pre- and retrochiasmatic mass, pushing up or perforating the hypothalamus, occupying the lower third of the third ventricle, and extending to the retroclival space (Fig. 2). At examination, the patient was neurologically intact and had normal vision and no hemianopsia. His height and weight were 1.24 m (−1 SD) and 22.7 kg (0 SD), respectively. Pubic hairs were present (P2). Dimensions of the testicles and of the penis were typical of a prepubertal status, measuring 45×28 and 55×25 mm, respectively. Endocrine investigations showed no pituitary deficit and no diabetes insipidus but confirmed a central precocious puberty [testosterone 5.70 ng/ml; peaks of follicle-stimulating hormone (FSH) and of luteinizing hormone (LH) at 2.8 and 12 μU/ml, respectively, during the LH-releasing hormone (LH-RH) test]. Neuropsychological tests [Wechsler Intelligence Scale for Children (WISC R)] confirmed that the child was in the normal range (global IQ of 116, verbal IQ of 111, and performance IQ of 118).

An attempt at total removal of the tumor was undertaken in March 1988. The surgical approach combined subfrontal, pterional, and trans-lamina terminalis routes, but failed to remove the whole tumor due to the severity of adherence with the chiasm, hypothalamus, and surprisingly, the arachnoid of the posterior fossa. Despite initial cyst decompression, use of the CUSA, progressive fragmentation of the calcified tumor, diverse changes in the surgical approach, and gentle traction on the tumor capsule, it rapidly became obvious that further dissection would imply severe neurovascular risks and that surgery should be stopped at that point. As shown on postoperative imaging, the volume of the residual tumor was not negligible (Fig. 3). The postoperative period was complicated by several problems: panhypopituitarism, diabetes insipidus, hypersomnia with inversion of the diurnal rhythm, bulimia with an impressive weight gain, and a dramatic behavioral change. Pituitary deficits and diabetes insipidus were easily corrected; sleep disorders were resolved in a month or two, but the need for food and behavioral disturbance persisted and even increased. Interestingly, the precocious puberty began regressing immediately after surgery, the testosterone level returning to normal 3 weeks postoperatively.

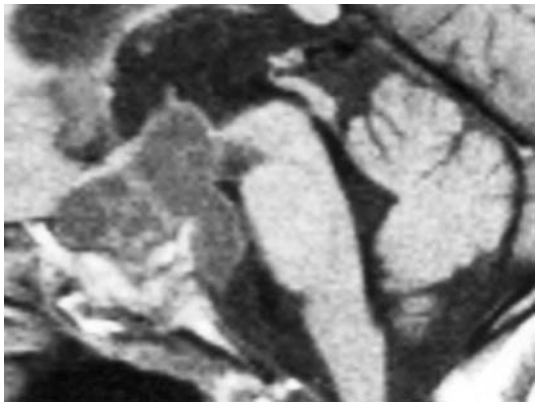

Fig. 2 Same patient. Preoperative MRI after contrast injection showing on a sagittal view the presence of a cystic intra- and suprasellar mass, extending into the third ventricle through the ventricular floor and into the posterior fossa

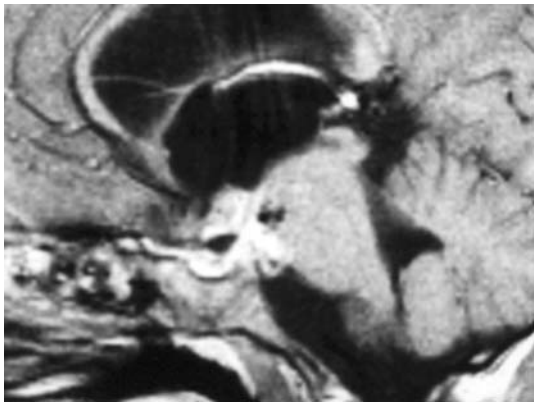

Fig. 3 Same patient. Postoperative MRI after contrast injection, showing on a sagittal view the persistence of a nonnegligible volume of CP

In July–August 1988, external conventional irradiation of the residue was given at a dose of 52 Gy.

During the following 14 years, socialization of the child became more and more problematic due to essentially two types of disturbances. The first was a perpetual compulsive bulimia, a real addiction to food, obscuring all other interests and activities and progressively leading the child to lie, to steal at home as well as from supermarkets, and to run away from home. The boy's weight remained more or less under control until he began refusing parental authority over his diet concurrent with the cessation of growth hormone (GH) replacement therapy whose lipolytic activity is well documented. He then weighed 115 kg at a height of 1.75 m. The second type of disturbance was characterized by markedly abnormal behavior with general disinterest, depression, outbursts of rage with self-directed aggression, social disinhibition, social withdrawal, attention disorders, a lack of motivation, and short-term memory impairment. As a result, academic difficulties began a few months postoperatively at the start of the new school year. Several neuropsychological tests were performed that remained generally the same over the following years, showing a normal global IQ around 100, a still good verbal IQ around 115, but a low performance IQ around 80. Very rapidly, normal schooling became impossible. Various medications, several psychiatric hospitalizations, psychotherapies, and diets failed to improve the patient's condition. Intracranial pressure (ICP) monitoring, indicated by persistently large ventricles, failed to demonstrate an increased pressure. The last MRI, more than 10 years postoperatively, showed the persistence of calcifications but a striking tumor regression compared to the initial residual tumor. At last, in contact with the family in 2004, the mother ended her letter with these words: "Our family, our marriage, our youngest child are in distress. What can the future be? What can I do to help my boy? Who can I see?"

The prospective series

The protocol

A protocol involving the neurosurgeons, endocrinologists, psychiatrists, and psychologists of our hospital was set up to study the clinical, endocrine, mental, and intellectual outcome of the children presenting with a CP as well as their eating behavior. Authorized parental consent was the only necessary prerequisite for the inclusion in the study. The patients were investigated pre- and postoperatively as completely as possible. Postoperatively, they were reassessed for 2 years every 6 months. It must be stressed, however, that the preoperative evaluation was difficult to complete in the case of emergency surgery or difficult to interpret in the setting of blurred vision or altered consciousness. In some cases, it was necessary to interview the parents and/or teachers in the place of formal neuropsychological testing. Similarly, some complex endocrine investigations could not be executed. Besides basic and routine neurological and imaging studies, investigations were as follows:

1. *Biological:* to determine the level of the anterior and posterior pituitary hormones and of insulinemia. Weight and height were systematically recorded.
2. *Psychometric:* to evaluate the psychomotor development of the child, the intellectual and academic level and memory using the WISC-R test, and appropriate memory and projective tests. The academic level was evaluated by schoolteachers.

Table 1 Symptoms constituent of the ventromedial hypothalamic psychosyndrome

Hyperphagia
Food-seeking behavior and short-lasting satiety
Increased reactivity to food stimuli
Obsessive thoughts about food
Low frustration tolerance for food
Irritability
Increased reactivity and sensitivity in social relationships
Temper tantrum
Outbursts of rage with self-injurious behavior or heteroaggressiveness
Conduct disorders
Lies, thefts, and runaways
Depressive symptoms
Sadness, social withdrawal
Loss of usual interests
Somatic complaints
School difficulties
Evident short-term memory impairment
Attention disorder
Motivation disorder

Table 2 Children's global assessment scale

Superior	91–100
Normal	81–90
Partial transitory disturbance	71–80
Partial permanent disturbance	61–70
Slight global disturbance	51–60
Severe global disturbance	41–50

Over 60, the daily functioning remains in the normal range. Below 60, the daily functioning is severely altered

3. *Behavioral:* to appreciate the socialization of the child and his eating behavior.

Symptoms that define the hypothalamic psychosyndrome were systematically sought (Table 1). Depressive symptoms, when present, were just noted but not quantified due to the lack of a reliable tool adapted to all ages. The global functioning of the child was scored using the Children's Global Assessment Scale (C-GAS) [which is an adaptation for children of the Global Assessment Functioning (GAF)] used in adulthood. The C-GAS is a scale from 0 to 100 (Table 2). It studies the repercussion of the behavioral disturbances on daily life. The normal range is from 80 to 100. A score of 60 to 80 indicates minimal acceptable social insertion. A score between 50 and 60 indicates severe behavioral impairment. A score below 50 indicates that the patient needs a specialized environment.

Material

Fourteen consecutive patients with CP were included in the study from 1994 to 1998. At admission, the median age of the patients was 7 years (range 4–13.6).

Of the 14 CPs, 12 were strictly retrochiasmatic and 2 were pre- and retrochiasmatic. In 11 cases, the tumor extended into the third ventricle and in 8 cases it reached the level of the foramen of Monro. All the CPs were calcified and had a more or less large cystic component.

All were treated surgically with the aim of removing as much of the tumor as possible. The surgical routes used differed according to the surgeon and the topography of the lesion. Eight children were operated on through a pterional interopticocarotid approach. In four, the pterional route was associated with a trans-lamina terminalis fenestration. The last two children had an interhemispheric trans-lamina terminalis approach.

An apparently "total" removal, confirmed on postoperative imaging, was achieved in 9 cases. In the remaining 5 children, surgery was stopped before being able to radically excise the lesion. Surgery went uneventfully in 13 of the 14 cases. In one case, it was complicated by a minor bleeding, which, although originating from the carotid artery, was easily controlled. From a neurosurgical point of view, the immediate postoperative follow-up was uncomplicated in all cases, the median time of hospitalization in our department being 8 days (range 3 to 10 days).

Results

At 2-year follow-up, only two children (14.3%) were symptom-free, considered as intellectually normal, and attending normal schooling. The 12 others presented with at least two of the six symptoms constituting the hypothalamic syndrome (Table 3).

1. Hyperphagia was noted in 85% of the children (n=12). It always appeared soon after surgery. At 6 months postoperatively, the gain in weight was greater than +3

Table 3 Behavior troubles developing in the first two postoperative years

Patient no.	Hyperphagia	Irritability	Hostility	Conducts disorders	Depressive symptoms	School difficulties	Severity index
1	+	+	+	+	+	+	6
2	+	+	−	+	+	−	4
3	+	−	−	−	+	+	3
4	+	+	−	−	−	−	2
5	+	+	+	−	−	−	3
6	+	+	−	+	+	−	2
7	+	+	−	−	−	−	2
8	+	+	+	−	+	+	5
9	+	+	+	+	+	+	6
10	+	−	−	−	+	−	2
11	+	+	+	−	+	−	4
12	+	+	−	−	+	−	3
13	−	−	−	−	−	−	0
14	−	−	−	−	−	−	0
Total	12	10	5	4	9	4	

Table 4 Evolution of BMI and C-GAS scores during the first year after surgery

Patient no.	Age at surgery	BMI before surgery (SD)	BMI 6 months	BMI, 1 year	C-GAS before surgery	C-GAS, +6 months	C-GAS, 12 months
1	5.3	0.25	9.20	10.96	95	40	40
2	13	1.80	2.86	4.21	75	40	55
3	13	2.05	3.04	5.35	60	45	45
4	13.6	−2.33	0.56	0.47	75	65	65
5	9	5.12	10.32	9.67	65	50	55
6	9.1	0.20	1.93	2.55	95	70	70
7	4.5	0.19	2.37	3.88	95	60	70
8	12.6	5.58	9.58	8.27	75	45	40
9	6.8	9.50	12.50	11.80	90	40	30
10	9.5	−0.50	1.23	2.09	100	85	80
11	7	3.21	5.01	6.49	90	55	60
12	6.5	1.06	9.11	11.18	75	40	55
13	4	1.40	6.65	5.98	95	85	80
14	4.5	0.45	1.22	1.57	95	90	85
Mean scores		+2.00	+5.4	+6.3	84.28	57.85	59.28

BMI Body mass index
C-GAS Children's global assessment scale, *SD* standard deviation

SD in 8 cases (57.1%) (Table 4). Seven (50%) of the 14 children of the series developed a real addiction to food and finished with a body mass index (BMI) greater than +5 SD (+5.35 to +11.8). All these children, when confronted with food, were hyperreactive to visual and olfactory stimuli. In 3 children, the search for food did not only occur during the daytime but also at night. From a qualitative point of view, the food ingested was usually rich in carbohydrates. Interestingly, 6 (42.8%) of the 14 children of the series had an abnormal BMI preoperatively. In 5 cases it was greater than +2 SD. In one child, it was equal to −2.6 SD. This child, cachectic before surgery, became hyperphagic immediately after, but not bulimic, so that her BMI never exceeded +0.5 SD.

2. Deleterious behavior developed at various degrees in 12 children (85%). Some were related to bulimia (n=4), like running away, theft, and lies but the majority was not (n=10, 71.4%), such as irritability, aggressiveness, and bursts of rage. In two children, the severity of these symptoms led to psychiatric confinement.
3. Affect disturbance, mainly depressive symptoms, was observed in 9 children (64.2%). In 6 of them, the symptoms were resolved in 6–12 months with the help of psychotherapy, but in the remaining 3 they persisted despite antidepressive therapy.
4. Cognitive deficiency was rare. For those of the patients who were evaluated both pre- and postoperatively, the IQs remained roughly the same. A memory deficit was noted in only one case and resolved spontaneously in a few months. Capabilities of understanding and reasoning were not altered even in the case of academic results declining (n=4).
5. Global functioning (Table 4) was over 60 in all children but one before surgery, but only in six children 2 years after treatment. The mean scores preoperatively, 6 months, and 24 months after surgery were 82.5, 52.9, and 55.4, respectively. The drop was greater than 25 points (30–60) in five patients. The postoperative scores of the C-GAS were significantly correlated (p=0.001) to the severity of the psychosyndrome (Table 5).

Table 5 Main correlation between behavioral, physical, and biological parameters

	C-GAS			BMI (SD)		
	Before surgery	6 months	1 year	Before surgery	6 months	1 year
Severity of psychosyndrome	−0.20	−0.84**	−0.91 **	0.57*	0.63*	0.68**
BMI (ds)						
Before surgery	−0.22					
6 months		−0.59*		0.76**		
1 year			−0.742**	0.67**	0.95**	
Insulinemia early after surgery	−0.64	−0.37	−0.54	NS	NS	NS

C-GAS Children's global assessment scale, *SD* standard deviation
*p<0.05; **p<0.001

Table 6 Details of insulinemia before and after surgery in the 14 children

Patient no.	BMI (SD) before surgery	Insulin before surgery	Insulin, 1–2 months	Insulin, 6 months	Insulin, 1 year	
1	0.25	–	21	47	–	Severe psychosyndrome without increase in insulinemia. Insulin remains low even with weight gain
2	1.84	–	–	109	706	Increased insulin but no preoperative data
3	2.05	506	237	1,065	519	Insulin is increased before surgery, like BMI
4	−2.33	147	240	403	513	Insulin increases early after surgery when BMI is very low
5	5.12	70	79	203	128	Insulin increases at 6 months
6	0.2	–	77	53	91	Normal values and moderate psychosyndrome
7	0.19	–	–	–	43	
8	5.58	285	211	–	–	Insulin is increased before and after surgery
9	9.05	–	174	308	–	Elevated insulin after surgery, severe psychosyndrome
10	−0.50	51	24	nd	72	Normal values
11	3.21	–	63	80	108	Normal-high values at 1 year
12	1.06	71	45	115	–	Normal-high values at 6 months
13	1.40	98	22	113	66	Normal-high values at 6 months
14	0.45	27	40	11	18	Normal values, no psychosyndrome

Values correspond to the peak of insulinemia after HGPT
BMI Body mass index, *SD* standard deviation

6. Insulinemia (Table 6) was increased preoperatively in 2 of 8 cases and postoperatively in 6 of 14 cases. The level of insulinemia was not correlated to the preoperative BMI.
7. Tumors on preoperative MRIs were extraventricular in 2 cases (Fig. 4) and intraventricular in 12 (Fig. 5). In the first 2 cases, the tumor removal was total. The postoperative MRIs confirmed the radical tumor resection and showed, in addition, the persistence of a clearly visible ventricular floor (Fig. 4). These 2 cases had a simple postoperative follow-up with no hypothalamic disorders. The 12 other patients had intraventricular CPs, and the postoperative MRIs constantly showed the disappearance of the ventricular floor (Fig. 5). All these patients presented with a more or less severe postoperative hypothalamic syndrome.

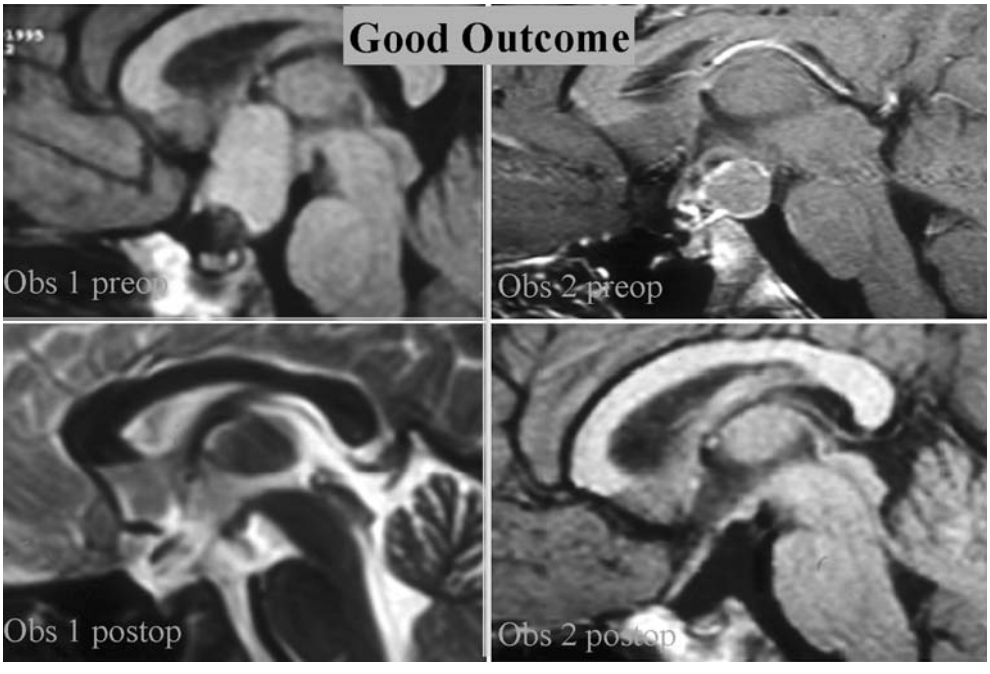

Fig. 4 Pre- and postoperative MRIs of the two children of the series with a good outcome. In both cases, the CP was extraventricular and the floor of the third ventricle preserved postoperatively

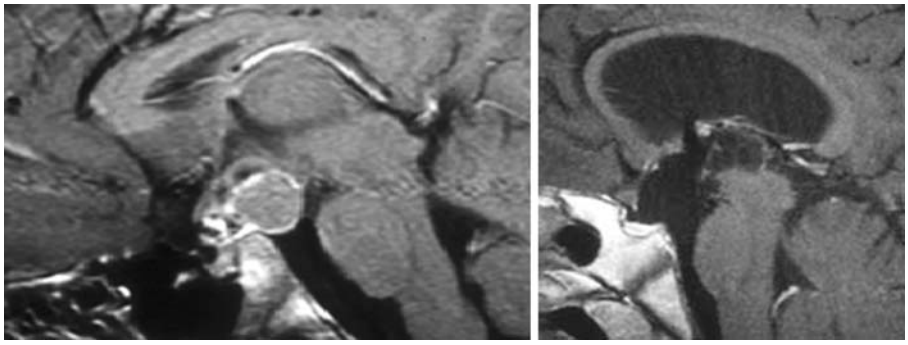

Fig. 5 CP extending into the third ventricle through its floor. *Left*, preoperative MRI sagittal T1 view after injection. *Right*, postoperative MRI sagittal T1 view showing a large defect at the level of the floor

Discussion

This series emphasizes the difficulty in treating childhood CPs and suggests that these tumors should not be all treated in the same way.

(1) At least in children, our series and the experience of many others [3, 5, 6, 11, 13–15, 18] show that transcranial attempt at total removal of CPs may be very harmful even in the absence of intraoperative complication or failure to achieve radical removal. This demonstrates that even apparently "gentle" tractions on the tumor capsule may mobilize the hypothalamus and induce lesions at its level.

(2) The hypothalamic syndrome is frequently severe, compromising patients' social and professional insertion. In many cases from our series, the intensity of the behavioral dysfunction made it necessary to withdraw the children from normal school and to confine some of them in psychiatric hospitals. Hyperphagia was the most frequent and impressive symptom. This symptom has been described for a long time [2, 4, 16] after hypothalamic lesions both experimentally and in medical practice. As observed in our patients, hyperphagia was frequently associated with affect [12, 17] or personality dysfunction. These disorders were extreme in the case of bulimia with aggressiveness, bursts of rage, or irritability. Cognitive function, on the contrary, did not seem to be affected by the hypothalamic syndrome, or only transiently. It is worth noting that contrary to some previous reports [1, 18, 19], the postoperative intellectual and memory capacities were preserved in our patients, meaning that postoperative academic failure, when present, resulted more from a behavioral dysfunction than from an understanding incapability.

(3) Human hypothalamic syndrome and symptoms observed experimentally after bilateral lesions of the ventromedial nucleus of the hypothalamus are very similar. In animals, these lesions cause an overstimulation of the parasympathetic nervous system [7, 9], which in turn induces a hypersecretion of insulin. For some authors [8, 20], this hyperinsulinism would be the primary cause of hyperphagia and obesity. In our study, several patients had abnormally high levels of insulin, a few before surgery and a greater number after surgery. Interestingly, the level of hyperinsulinemia was not correlated to the BMI. This finding suggests, first, that hyperinsulinism was not secondary to the excess of weight but was a primary phenomenon, and second that hyperinsulism, because inconstant, was only one of the possible mechanisms leading to hyperphagia.

(4) As already emphasized by De Vile et al. [3] and Hayward et al. [5], treatment of CPs should be tailored case by case depending upon the relationship of the tumor with the hypothalamus. Of the 14 children in the present series, 2 were "normal" postoperatively, whereas the remaining 12 were affected by a more or less severe hypothalamic syndrome. Interestingly enough, the two with a good outcome had a normal BMI preoperatively and, on MRIs, an extraventricular tumor, indicating that the hypothalamus was intact preoperatively. This is probably the reason why total removal was achieved without drama. In both cases, MRIs after surgery actually confirmed the apparent preservation of the floor of the third ventricle. On the contrary, the remaining 12 cases of our series with a poor outcome had preoperatively clinical and/or radiological findings, indicating an already hypothalamic involvement. Four of these children had a BMI superior to +3 SD, and one was cachectic, another form of hypothalamus deregulation. On MRIs, all the tumors in this subgroup of patients extended within the third ventricle, sometimes reaching the foramen of Monro and causing hydrocephalus, all giving the feeling that the ventricular floor was disrupted. Postoperative MRIs in these 12 patients constantly showed the disappearance of the ventricular floor. For De Vile et al. [3] and Hayward et al. [5], CPs must be divided into two groups and treatment adapted to each of them. We fully agree with this opinion. CPs that do not involve the hypothalamus, i.e., those with a normal or only slightly increased preoperative BMI, no behavioral dysfunction, and no intraventricular extension are amenable to radical excision. On the contrary, those with an obviously preoperative hypothalamic involvement, i.e., mainly those with abnormal BMI, behavioral disturbances, and/or intraventricular extension are not amenable to "total" resection. Once this is kept in mind, the treatment of these intraventricular tumors must be adapted to the anatomical form of the tumor, the surgeons' experience, and the facilities offered in each center. When the tumor is solid or poorly

cystic, there is no other choice but to remove part of it via a transcranial or a transsphenoidal route [10, 13], the goal being to decompress the optic pathways and reduce the tumor volume. More options are given when the tumor is cystic; the cyst could possibly be withdrawn through a coronal reservoir or sterilized by the intracystic injection of bleomycin or isotopes. Incomplete removal exposes to recurrence. We now know the efficiency of irradiation, either gamma knife when the residue is solid and separated from the optic pathways or external and conformational. Being now aware of the possible side effects of total removal in the case of intraventricular CPs, we have changed our policy of treatment and decided to tailor the treatment case by case, grossly following the paradigm of treatment proposed by Hayward et al. [5].

Conclusions

Radical surgery is probably the best treatment when CPs are extraventricular, i.e., when preserving the floor of the third ventricle. In these cases, postoperative follow-up is compatible with an acceptable social, academic, and professional life. Radical surgery, on the contrary, is contraindicated when CPs are intraventricular. Postoperative follow-up in such cases has the greatest chances to be then complicated with the development of a hypothalamic syndrome, which will prevent the patient from having an acceptable life. Treatment of these lesions is extremely complex, associating at diverse degrees surgery, irradiation, and chemotherapy.

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