Liste des abréviations

GVO	Gliome des Voies Optiques
CPP	Comité de Protection des Personnes
BB-SFOP	Baby Brain- Société Française d'Oncologie Pédiatrique
OPG	Optic Pathway Gliomas
NF1	Neurofibromatosis type 1
BMI	Body Mass Index
MRI	Magnetic resonance imaging
IGF1	Insulin-like growth factor-1
IGFBP3	Insulin-like growth factor-binding protein 3
fT4	Free Thyroxine
TSH	Thyroid-stimulating hormone
ACTH	Adréno Cortico Trophic Hormone
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
DHEA-S	Dehydroepiandrosterone sulfate
GH	Growth hormone
GHD	Growth hormone deficiency
DDAVP	Deamino-8-D-arginine-vasopressin (=Desmopressin Acetate)
rhGH	Recombinant human Growth Hormone
GnRH	Gonadotropin-releasing hormone
SDS	Standard Deviation Score
OR	Odds Ratio
RT	Radiotherapy
CT	Chemotherapy
LGG	Low Grade Glioma
ICH	Intracranial hypertension

Plan

ABSTRACT

Long-term endocrine disorders in children treated initially by chemotherapy for optic pathway glioma and evaluation of predictive factors of these sequelae: A multicentric study using the national protocol from the French Society of Pediatric Oncology (BB-SFOP protocol).

Department of Pediatric Oncology, University Hospital,

Background. Therapeutic approach favors chemotherapy as the first-line-treatment in symptomatic Optic Pathway Gliomas (OPG) in order to delay the use of radiotherapy and surgery and decrease the sequelae of such treatments. There are few data on long term endocrine outcomes of OPG treated by upfront chemotherapy.

Objective. To describe the long-term endocrine disorders in these patients and to identify potential early predictors of the endocrine involvement.

Patients and method. All the children diagnosed with OPG at an age younger than 16 years, treated with upfront chemotherapy according to the BB-SFOP protocol in France between June 1990 and December 2004, and registered in the French national BB-SFOP registry were included. The protocol consisted of a 16-month polychemotherapy regimen with seven cycles of carboplatin, procarbazine, etoposide, cisplatin, vincristine, and cyclophosphamide. In case of uncontrolled tumor, the children received further treatment (chemotherapy, surgery, radiotherapy). All underwent a late evaluation with clinical and hormonal pituitary assessment between September 2011 and March 2016.

Results. One hundred and two patients were included in our study. The mean age at diagnosis was 3.3 ±0.3 years and mean time of follow-up was 13.9 ± 3.7 years. At last evaluation, 36% of the patients had a history of precocious puberty, 46% had obesity, 74% had growth hormone deficiency, 57% thyrotropin deficiency, 36% corticotrophin deficiency, 33% hypogonadotropic hypogonadism, 30% hypergonadotropic hypogonadism, and 15% central diabetes insipidus. When chemotherapy was used alone (with no radiotherapy and no surgery), it was protective of late endocrine sequelae.

Conclusion*.* Obesity and late endocrine dysfunction were frequently found in subjects treated by upfront chemotherapy for OPG during childhood. Chemotherapy when used alone was protective of endocrine sequelae, further underlining that the avoidance of radiotherapy and surgery, if possible, may spare pituitary function.

INTRODUCTION

Childhood brain tumors are the most common pediatric solid tumor [1]. Pilocytic astrocytoma (World Health Organization grade 1) is one of the most common childhood brain tumors, representing about 17% of all brain tumors [2]. Optic Pathway Gliomas (OPG) are histologically benign tumors that typically develop during early childhood. They comprise almost 5% of all brain tumors in children [3]. Most of them are pilocytic astrocytomas [4], and about 30% of these cases occur in children with Neurofibromatosis type 1 (NF1) [4-6].

Clinically they can be classified into sporadic tumors arising in individuals with or without a pre-disposing condition. Sporadic tumors typically arise within the chiasmatic-hypothalamic region or in other brain structures adjacent to, or involving the optic tract; they do not typically involve the optic nerves. OPG associated with NF1 characteristically involve optic nerve, chiasm and optic radiation, including the geniculate ganglion [7].

The natural history of OPG is unpredictable, with the possibility of spontaneous involution. They constitute a chronic disorder subject to periods of quiescence and progression during childhood and adolescence. It has been shown that they have the greatest tendency to grow in the first 3-5 years of life [7, 8]. The median age at presentation in childhood is about 5 years, and sexes are equally affected. Diagnosis symptoms depend on the location: usually ophthalmological and neurological disorders, in other cases cachexia or endocrine signs, dominated by precocious puberty [9]. Glioma can also be discovered by a systematic MRI performed in children with NF1. In France, the follow-up of NF1 patients is proposed by neuro and oncopediatrician within the NF-France network. It relies upon annual ophthalmologic monitoring including measurement of visual acuity and visual field, and cranial MRI in case of abnormality. When insufficient cooperation makes ophthalmologic examination difficult, either because of age (under 6 years) or due to cognitive disorders, brain MRI is systematic, and will be performed every two years.

Only symptomatic and evolutive OPG require a treatment. To evaluate the evolutivity of the tumor, the following monitoring is proposed: ophthalmologic examination and cranial MRI at 3 months, 6 months, 12 months, 18 months, then every

year until the age of puberty [10-12]. Children with NF1 usually have a more indolent course. Tumors may grow more slowly or occasionally regress spontaneously. Conversely, over 90% of children with OPG without NF1 will require some form of therapy. [13]

Surgery is one possible initial therapeutic strategy when the tumor is limited to one optic nerve with severe visual loss, however when the tumor involves the optic chiasm the risk of inducing vision loss and/or hypothalamic disorders is high. Currently the initial role of surgery is mainly biopsy for tissue diagnosis and relief of the hydrocephalus if present [16, 17]. Radiotherapy is not recommended in the first place except in extreme cases (patients with a voluminous tumor inaccessible to surgery). It has been shown that radiotherapy increased the risk for vascular complications and high grade second tumor, specifically in young children and NF1 patients [14, 15].

The French Society of Pediatric Oncology (SFOP) developed, from 1990, a BB-SFOP chemotherapy regimen (Baby Brain-French Society of Pediatric Oncology) that was initially specifically designed for children under 5 years of age [18] and then extended in 1995 to children over 5 years of age, including those with NF1 given the specific toxicity of radiation in this type of disorder. This treatment included a combination of 6 antimitotics that are administered sequentially for 16 months and included carboplatin, procarbazine, etoposide, cisplatin, vincristine and cyclophosphamide. This chemotherapy was mainly intended to delay or even to avoid irradiation of the tumor. Currently, therapeutic approach favors chemotherapy as primary treatment in progressing OPG, using most commonly carboplatin and vincristine as the first-line [19]. There are few data on long term outcomes of OPG treated by upfront chemotherapy.

Overall survival in children with OPG has been recently described as less favorable as previously thought when follow-up is long enough (more than 10 years after diagnosis) with 75.5% survival at 18 years [5]. Endocrine and metabolic sequelae have been found among survivors [20-22, 25], even more than 15 years after the diagnosis [26-30]. In numerous studies, OPG patients have been mixed with other cranial tumors of the area, making difficult to precisely identify these patients and specify their prognosis. In one study identifying OPG and hypothalamic and suprasellar gliomas with surgery and radiotherapy as main treatments, long term endocrine sequelae have been

shown in 54.8% of the patients [31]. Endocrine function among these patients may be affected either by the direct impact of the tumor on the hypothalamic-pituitary axis or secondarily as a consequence of treatment with surgery and/or radiotherapy and/or chemotherapy [17, 32-34]. Damage by cranial irradiation is well established [14, 27]. The effects are delayed and may appear many years after therapy. Growth hormone axis is the most sensitive of the hypothalamic functions to radiation [32, 35-39], but gonadotropin, corticotrophin and thyrotropin secretion may be compromised.

This high rate of endocrine sequelae (among others) was part of the reasons for the proposal of chemotherapy as the first line treatment in these patients. Little information is available regarding long term endocrine outcomes specifically after upfront chemotherapy in children with symptomatic OPG. In a recent study analyzing centrally located low grade glioma (comprising OPG) with mostly chemotherapy as initial treatment, a significant association between age and growth hormone deficiency and hypothyroidism has been revealed, but location of glioma was not a predictor of endocrine involvement [40]. Another recent study, with a cohort of 65 patients with OPG treated essentially with chemotherapy and followed on a 32 months period, reported that OPG involving the hypothalamus and chiasm had endocrine dysfunction, while those involving the optic nerve alone or extending anterior to the chiasm had isolated visual deficits [16].

Using the French data base BB-SFOP (which lists all the children treated in France with BB-SFOP chemotherapy, regardless of the type of brain tumor), we isolated patients with OPG, and proposed in all patients from the data base treated between June 1990 and December 2004 (n = 182) a long-term assessment including clinical evaluation (height, weight, body mass index, pubertal stage), record of endocrine replacement treatments (recombinant human growth hormone, levothyroxine, hydrocortisone, androgens, estrogens, oestro-progestatives, recombinant human hCG and FSH, and desmopressin), and measurement of serum electrolytes (Na, K, Cl-, HCO3-), calcium, phosphorus, magnesium, IGF1, IGFBP3, free T4, TSH, prolactin, 8am plasma ACTH and cortisol, dehydroepiandrosterone sulfate (DHEA-S), FSH, LH, testosterone, oestradiol. We also recorded data from all MRI performed at diagnosis and during the follow up and used a recent protocol of classification [41] to determine a possible influence of location

on endocrine involvement. Our main objective was to describe the long-term endocrine disorder in these patients and to identify potential early clinical and radiological predictors of the endocrine involvement.

PATIENTS AND METHOD

Patients and chemotherapy regimen

The study included children diagnosed with OPG at an age younger than 16 years, treated with upfront chemotherapy according to the BB-SFOP protocol in France between June 1990 and December 2004, and who had a late endocrine evaluation between January 2011 and March 2016. OPG diagnosis was based on MRI findings (mainly T1-hypodense, T2-hyperdense lesion, with enhancement after gadolinium injection in the optic area) and/or histology when surgery was considered safe and necessary (for instance in cases with no NF1, or in case of diagnostic doubt). The French database BB-SFOP together with records from 20 pediatric oncology centers were used (Angers, Bordeaux, Brest, Caen, Clermont-Ferrand, Grenoble, Lille, Limoges, Lyon, Montpellier, Nancy, Nantes, Paris-Curie institute, Paris-Villejuif-Gustave Roussy Institute, Rennes, Rouen, St Etienne, Strasbourg, Toulouse, Tours). Chemotherapy consisted of seven cycles of three courses (A, B, and C) of two different drugs. The planned duration of chemotherapy was 16 months. In course A, patients received carboplatin 15 mg/kg (450 mg/m2) in a 1-hour infusion on day 1 and procarbazine 4 mg/kg/d (120 mg/m2/d) orally on days 1 to 7. In course B, patients were administered etoposide 5 mg/kg/d (150 mg/m2/d) in a 1-hour infusion on days 22 and 23, and cisplatin 1 mg/kg/d (30 mg/m2/d) in a 3-hour infusion with mannitol plus saline on days 22 and 23. In course C, patients received vincristine 0.05 mg/kg (1.5 mg/m2) on day 43 and cyclophosphamide 50 mg/kg (1,500 mg/m2) in a 1-hour infusion on day 43. The next cycle was started on day 64. Doses were calculated in milligrams per square meter for children older than 3 years. The cumulated doses of each drug were 3,150 mg/m2 for carboplatin, 5,880 mg/m2 for procarbazine, 2,100 mg/m2 for etoposide, 420 mg/m2 for cisplatin, 10.5 mg/m2 for vincristine, and 10.5 g/m2 for cyclophosphamide. The specific regimen of chemotherapy applied here has been described elsewhere [18]. Chemotherapy was indicated if there was clinical (significant deterioration of vision or new neurologic signs) and/or radiological tumor progression. Children who initially underwent partial surgery or biopsy before the initiation of chemotherapy were included (as their main initial treatment aimed at cure still was chemotherapy), whereas those with gross-total or

subtotal resection, other chemotherapy, or radiotherapy before BB-SFOP protocol were excluded.

The data base included data from medical records, including laboratory and radiology findings. Data corresponding to the late assessment were collected from September 2011 to March 2016. For each patient, data were reviewed, from the time of diagnosis to the latest contact.

Age, gender, NF1 status, intra-cranial hypertension, height, weight, BMI, cachexia (BMI < - 2 SD score and/or abnormal loss of weight), endocrine evaluation (precocious puberty, pituitary insufficiency, diabetes insipidus) and hormonal treatments (GnRH agonist for precocious puberty, rhGH, levothyroxine, gonadal steroids, DDAVP treatments) were recorded, at diagnosis, at the onset and at the end of BB-SFOP chemotherapy, in the time between the end of BB-SFOP chemotherapy and the last evaluation.

At the last evaluation, age, height, weight, BMI, and hormonal treatments were recorded. In addition, all the patients underwent a systematic measurement of serum electrolytes, IGF1, IGFBP3, free T4, TSH, prolactin, 8am plasma ACTH and cortisol, DHEA-S, FSH, LH, estradiol (female) or testosterone (male).

Adult age was defined with an age more than 18 years for males and more than 16 years for females.

Weight and height were converted in standard deviation (SDS) and body mass index (BMI) in Z-score according to french reference data [42, 43]. Denutrition was defined as BMI Z-score < - 2 SDS. Obesity was defined as BMI Z-score > 2 SDS.

Growth hormone deficiency (GHD) diagnosis was based on a history of GH treatment during childhood, actual GH replacement, and/or circulating IGF-1 level < -2SDS at last evaluation (according to age, gender, and pubertal stage). Most of the patients had growth hormone provocative tests but the results were not systematically recorded.

Thyrotropin deficiency was diagnosed if the patient received levothyroxine, and/or had circulating free T4 level < -2 SDS (<10 pmol/L) [44-47].

Corticotrophin deficiency was diagnosed if the patient received hydrocortisone at time of the last evaluation, and/or had circulating 8am plasma cortisol level below 6 µg/dL and

circulating ACTH levels below – 2 SDS (<10 pg/mL), and/or circulating S-DHEA < 0.6 mg/L for subjects aged more than 16 years [48].

Precocious puberty was diagnosed if sexual development began before the age of 8 years in girls and 9 years in boys, and/or if GnRH agonist was required.

Hypogonadotropic hypogonadism was diagnosed if patients received gonadal steroids (except oral contraceptive in women), and/or had circulating FSH and LH level < - 2 SDS in patients older than 17 years (FSH <1 UI/L and LH < 0.7 UI/L) and/or had circulating testosterone < - 2 SDS in boys older than 17 years (<3 ng/mL).

Hypergonadododotropic hypogonadism was diagnosed if circulating FSH and LH levels were > 10 UI/L and >5 UI/L, respectively.

Diabetes insipidus was diagnosed if patients received desmopressin therapy or had plasma sodium > 143 mmol/L (> + 2 SDS). Inappropriate AVP secretion was diagnosed if patients had plasma sodium < 135 mmol/L (< - 2 SDS) with no interfering treatment.

Hyperprolactinemia was considered if circulating prolactin was > 20 ng/mL.

Treatment modalities were recorded as partial surgery or biopsy before the initiation of BBSFOP chemotherapy, and subsequent chemotherapy or radiotherapy or surgery as a second line of treatment after BBSFOP chemotherapy because of insufficient tumor control. Surgical procedures for intracranial hypertension were also recorded.

MRIs performed at diagnosis and during the course of the disease were collected and centrally reviewed by two radiologist using a new approved interpretation protocol based on Dodge and modify Dodge classifications [49, 50] plus relevant and reproducible additional items [41], thus allowing comparison. This classification includes the five segments of the optic pathway : optic nerve, prechiasmatic, chiasmatic, retrochiasmatic and optic tracts and related lesions : hypothalamic involvement, pituitary gland involvement, pituitary stalk involvement, brain stem involvement, forebrain involvement, leptomeningeal dissemination, other sites of brain disease, and ventricular dilatation, (Figure and Table are shown in Annexe I)

The protocol was approved by our institutional review board (CPP Comité de Protection des Personnes—Ouest 3, Poitiers). Data were anonymized. All parents or legal guardians of the patients, as well as patients over 18 years gave their written informed consent.

Statistical analysis

Variables were expressed as means ± SD for continuous variables and percentages for discrete variable. Simple and multiple backward logistic regression analyses were performed to determine the best combination of predictors of late endocrine involvement and late obesity. Somatotropic deficiency, thyrotropin deficiency, corticotrophin deficiency, hypogonadotropic hypogonadism, hypergonadotropic hypogonadism, diabetes insipidus, and obesity (BMI > + 2 SDS) at late evaluation were used as dependent variables in simple, then multiple logistic regression analyses (0 = no deficiency; 1 = deficiciency). Simple logistic regression analyses were performed to determine odds ratios for early clinical and cranial MRI predictors (at diagnosis: age, gender, NF1 status, cachexia, obesity, precocious puberty, hormone replacement, anatomical involvement on cranial MRI), and for therapeutic predictors (second line chemotherorapy, radiotherapy, surgery procedures). Lastly, multiple backward logistic regression analyses were performed using variables with $P < 0.15$ from the simple regression analyses. For each variable, 0 to 10 values were missing. Multiple imputation with data augmentation was also performed to impute missing data. Thirty imputations using a sequential chain of iterations were performed. The assumption of this multiple imputation process is that data are missing at random. Logistic regressions were performed on imputed data as well as on the original data set, and odds ratios were considered significant only when found so both on the original data set and the imputed data. Significance was defined as $P<0.05$. All analyses were two tailed and performed with the SPSS 19 statistical package.

RESULTS

1-Description of the cohort

1-1-Characteristics of the whole cohort

One hundred and two patients from 182 patients aged less than 16 years who have been treated for OPG using BB-SFOP chemotherapy as the first-line treatment had a late clinical and hormonal evaluation. Eighty patients were excluded from the analysis because of missing endocrine data at diagnosis or during the follow-up. The flow chart is shown in Figure 1.

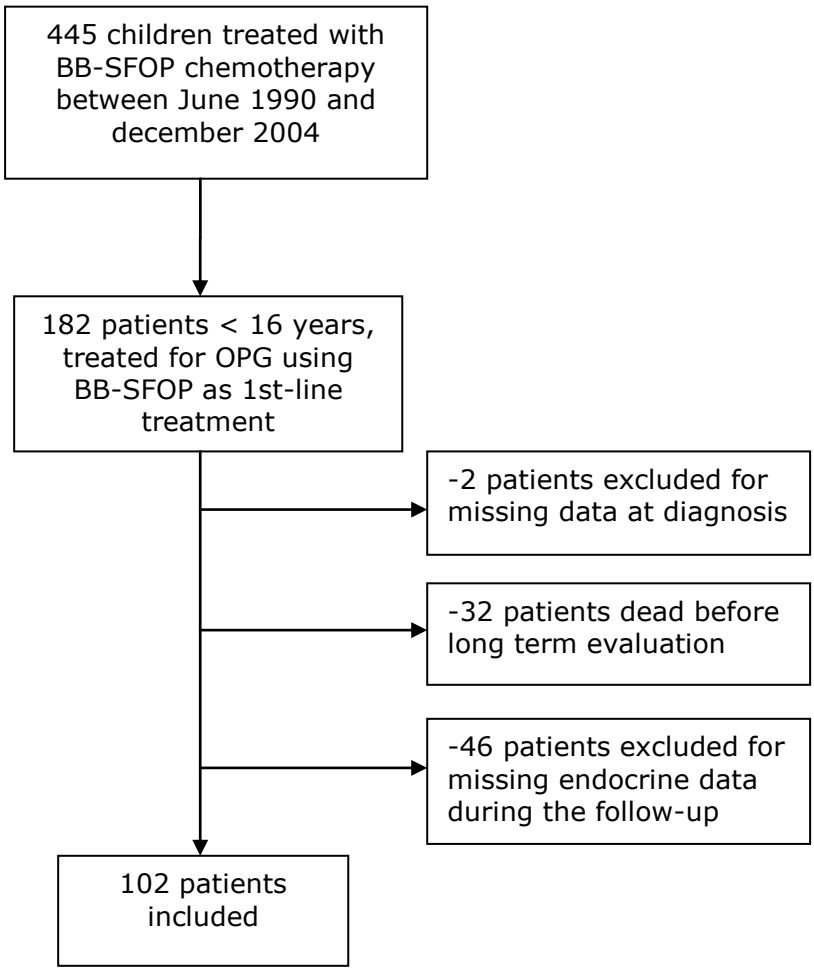


Figure 1. Flow chart

1-2- Characteristics of the patients at diagnosis and at the end of BB-SFOP chemotherapy

Patient's characteristics at diagnosis and at the end of BB-SFOP chemotherapy were reported for the whole cohort in Table I. The patients with late clinical and

endocrine evaluation were similar to those with missing data (therefore not included). The patients deceased before late evaluation had a high rate of cachexia, intracranial hypertension, and endocrine disorders at diagnosis, and a high rate of endocrine disorders and obesity after BB-SFOP chemotherapy.

Table I. Characteristics of the patients at diagnosis and/or before BB-SFOP chemotherapy, and at the end of BB-SFOP chemotherapy.

Initial characteristics	Patients with long term clinical and endocrine evaluation	Patients with missing data long term evaluation	Patients deceased before long term evaluation
AT DIAGNOSIS	102	46	32
Age (yrs)	3,3 ± 3,0	3,6 ± 3,1	2,6 ± 3.4
Male/Female (N)	49/53	24/22	11/21
NF1	38.2%	39,1%	31.2%
Intracranial hypertension	25,5%	21,7%	37,5%
Weight (kg)	16.32 ± 11.16	21.57 ± 18.95	15,75 ± 11.91
Weight (SDS)	0,43 ± 3,24	-0.21 ± 2,06	-0,35 ± 2.20
Height (m)	0,97 ± 0,25	1,10 ± 0,36	0,98 ± 0,39
Height (SDS)	0,77 ± 1,84	0.56 ± 0.78	0,51 ± 1,42
Body mass index (kg/m²)	15,98 ± 2,86	16.86 ± 4.00	16.2 ± 3.22
Body mass index (Z score)	-0,16 ± 2,11	0.68 ± 3,33	-0,01 ± 2.42
Cachexia	17.9%	8.6%	39.3%
Obesity (BMI > + 2 SDS)	15%	15%	18.8%
Endocrine disorder	6.2%	8.3%	12,5%
At the end of BB-SFOP chemotherapy (N)	102	46	32
Age (yrs)	4,6 ± 3,2	5,1 ± 3,1	4,3 ± 3,9
Weight (kg)	21,10± 14,22	24,47 ± 10,25	20.40 ± 13.03
Weight (SDS)	1,14 ± 3,73	2.23 ± 2,79	0.47 ± 3.34
Height (m)	1,07 ± 0,24	1,19 ± 0,20	1,05 ± 0,25
Height (SDS)	0,52 ± 1,77	0.76 ± 1.24	-0.28 ± 1.51
Body mass index (kg/m²)	17,04 ± 3,42	17,33 ± 2.11	17.86 ± 3.18
Body mass index (Z score)	0,57 ± 2,36	1,30 ± 1,82	0.81 ± 2.31
% of subjects with BMI < - 2 SDS	18.8%	0%	6.6%
Obesity (BMI > + 2 SDS)	22.6%	36.8%	33.3%
Endocrine disorder	19.3%	22%	33.3%

Endocrine disorders were found at diagnosis in 6.2% of the 102 patients with long term data: three had central precocious puberty, one GHD, one hypogonadotropic hypogonadism and one central diabetes insipidus. The mean time between diagnosis and first course of BB-SFOP chemotherapy was 3.9 ± 10.6 months. At the end of BB-SFOP chemotherapy, endocrine disorders were present in 19.3% of the children: three had central precocious puberty, seven had diabetes insipidus, three GHD, seven thyrotropin deficiency, three corticotrophin deficiency, and two had hypogonadotropic hypogonadism.

1-3-Cranial MRI characteristics of the 102 patients at diagnosis

On diagnosis MRI, 90.4% of the patients had hypothalamic involvement, 2.4% had pituitary gland involvement, 19.3% had pituitary stalk involvement and 42.2% had ventricular dilatation. Optic pathways involvement was detailed Figure 2.

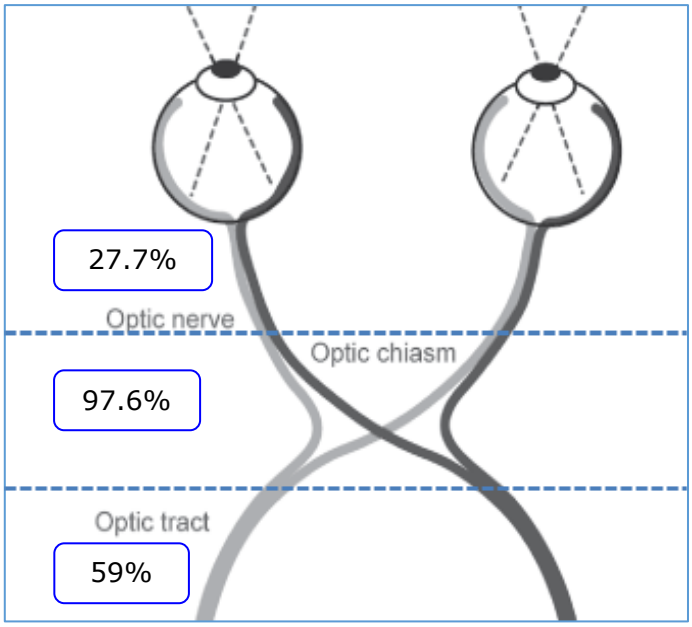


Figure 2. Optic pathways involvement on diagnosis cranial MRI

2-Intermediate evaluation

2.1-Endocrine disorders

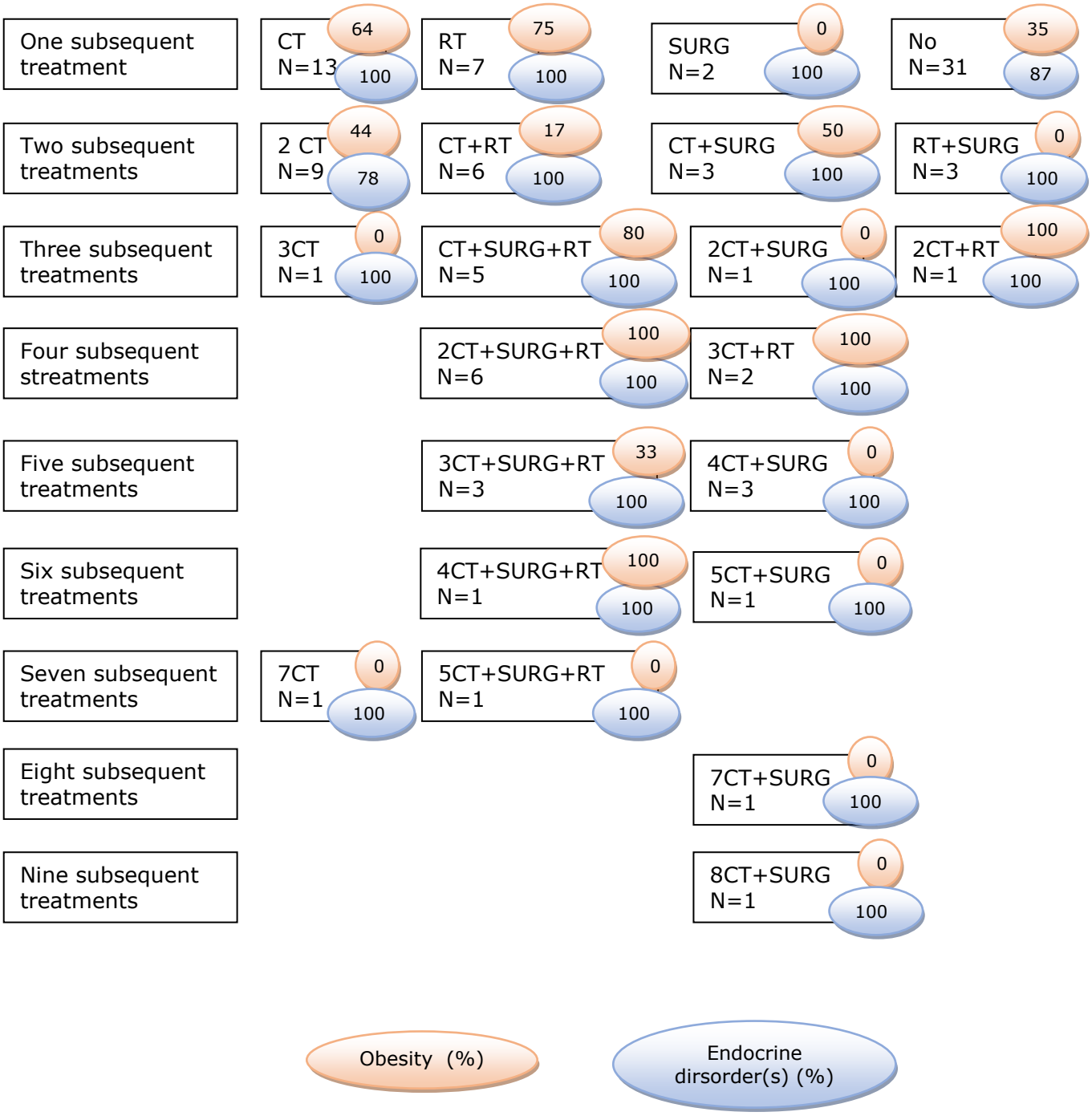
Sixty seven patients had one or more endocrine disorders between the end of BB-SFOP chemotherapy and last evaluation: twenty seven developed central precocious puberty, thirty one GHD, thirty seven thyrotropin deficiency, nineteen corticotrophin deficiency, eight hypogonadotropic hypogonadism, and seventeen central diabetes insipidus.

2.2-Subsequent therapies

Seventy-four patients completed BB-SFOP chemotherapy regimen, 13 stopped before the end because of tumor progression, 8 because of no tumor response (all received subsequent surgery and/or radiotherapy and/or chemotherapy treatment), 1 because of chemotherapy toxicity, 2 for parental refusal and 4 for other reasons. Mean duration of BB-SFOP chemotherapy was 12.7 ± 5.6 months.

Thirty-one patients received only BBSFOP-chemotherapy. In 59 patients, one to eight courses of subsequent chemotherapy was administered following BB-SFOP chemotherapy. Chemotherapy courses applied after BB-SFOP chemotherapy included Packer regimen (Vincristine and Carboplatin), Vinblastine, SIOPP LGG, Bevacizumab-Irinotecan, Hydroxyurea, Cisplatin-Etoposide, Temozolomide**,** TPCV (Thioguanine, Procarbazine, Lomustine, and Vincristine), Vinolo protocol (Vinblastine and Nilotinib), among others. Thirty five patients needed radiotherapy after BB-SFOP chemotherapy because of tumor progression, at a mean age of 9.03 ± 4.01 years, with radiation doses ranging from 44 to 56 gray. Thirty-one patients required surgery after BB-SFOP chemotherapy (for partial or subtotal tumor resection). The details of all subsequent therapies applied after BB-SFOP chemotherapy was shown in Figure 3 (and in a supplementary Table in Annexe II).

In addition, thirty six patients required a shunt and/or shunt revision (from one to nine procedures) for intracranial hypertension performed before, during or after BB-SFOP chemotherapy. Their association with late obesity and late endocrine disorder(s) were shown Figure 4.



SURG: Surgery

Figure 3. Subsequent therapies applied after BB-SFOP chemotherapy, and percentage of late obesity and endocrine disorder(s)(precocious puberty excluded).

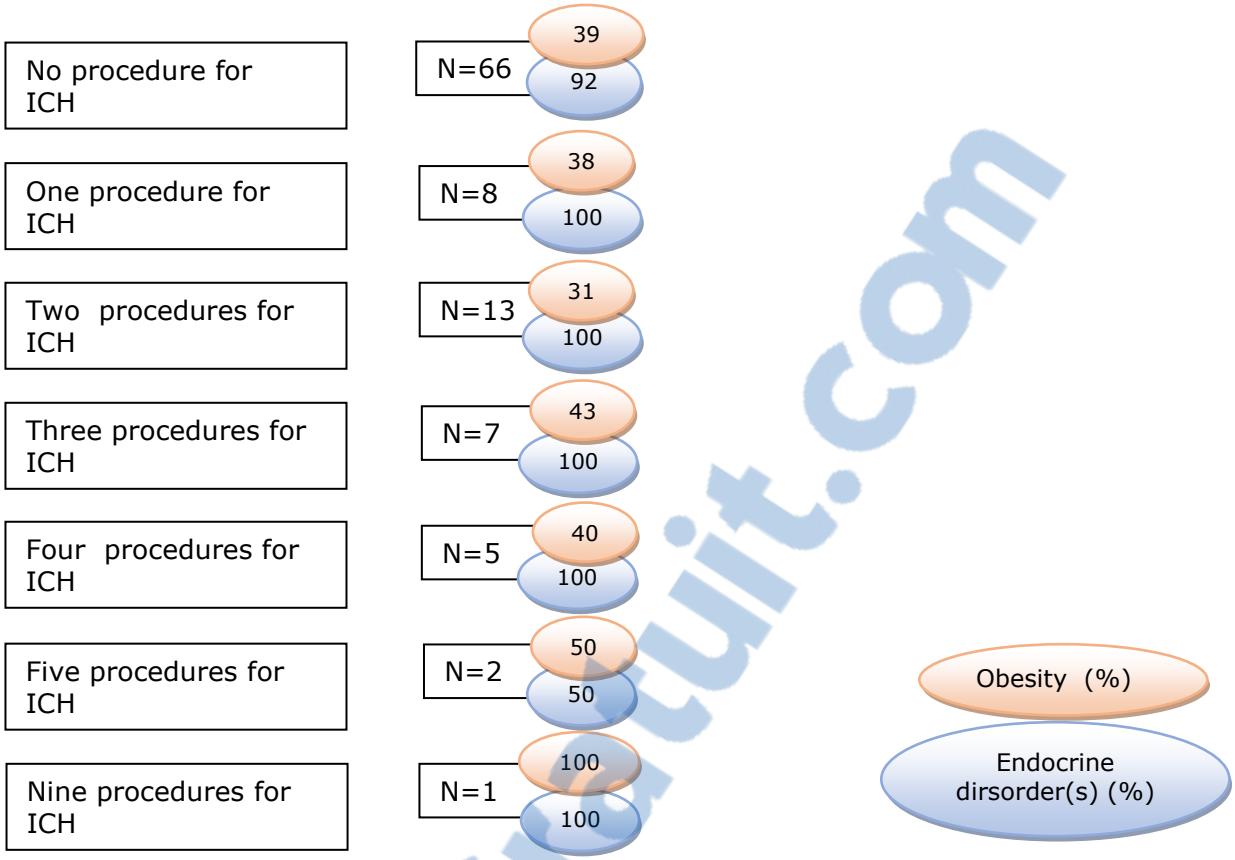


Figure 4. Surgical procedures for intracranial hypertension (ICH) applied before, during or after BB-SFOP chemotherapy, and percentage of late obesity and endocrine disorder(s).

3. Late evaluation

3.1-Clinical characteristics of the patients at last evaluation

The mean time between the diagnosis and last evaluation was 13.9 ± 3.7 years. Mean age at final evaluation was 17.1 ± 4 years. Four patients died after the endocrine evaluation, between the age of 14.7 and 22.7 years old, because of tumor progression (all had endocrine disorder(s): one with GHD, one with corticotrophin deficiency, one with central diabete insipidus and one with combined central diabete insipidus and thyrotropin and corticotrophin and gonadotropin deficiencies). Clinical characteristics and endocrine disorders at last evaluation were detailed in Table II. Twenty-five males and twenty-six females were at adult height at last clinical evaluation: mean adult height and weight were 1.68 ± 0.08 m (-1.1 ± 1.3 SDS) and 79.4 ± 31 kg (1.1 ± 4.5SDS) in males and 1.58 ± 0.08 m (-0.7 ± 1.4 SDS) and 64.4 ± 19.1 kg (2.1 ± 3.4SDS) in females: 15.4% of females and 20% of males had adult height two or more standard deviations below population norms.

Table II. Clinical characteristics of the patients at last evaluation

	all (n=102)	male (n=49)	female (n=53)
Age (years)	17,1 ± 4	18,1 ± 3,9	16,2 ± 3,9
Weight (kg)	61.5 ± 24.5	67,4 ± 29,4	56,9 ± 19,1
Weight (SDS)	1,7 ± 3,6	1,5 ± 4,2	1,9 ± 3,0
Height (m)	1.57 ± 0.13	1,62 ± 0,14	1.52 ± 0.11
Height (SDS)	-0,96 ± 1,50	-1,1 ± 1,7	-0,8 ± 1,3
Delta height(SDS)*	-1.75 ± 2.1	-2 ± 2.8	-1.6 ± 1.6
Body mass index (kg/m²)	23.9 ± 6.2	24.0 ± 6.5	23.8 ± 6.1
Body mass index (Z-score)	2,5 ± 3	2.0 ± 2.7	2,6 ± 2,9
Subjects with BMI < - 2 SDS	1.2%	2.6%	0%
Subjects with BMI > + 2 SDS	46%	42.1%	49.0%
History of central precocious puberty	35.6%	38.1%	33.3%
Endocrine disorder	94,1%	98.0%	90.6%
GH deficiency	73.9%	78.0%	70.2%
Thyrotropin deficiency	56.7%	56.5%	56.9%
Corticotrophin deficiency	36.1%	35.4%	36.7%
Hypogonadotropic hypogonadism	33.3%	30.2%	36.4%
Hypergonadotropic hypogonadism	29.8%	46.5%	12.2%
Central diabetes insipidus	14.8%	17.1%	12.8%
Inappropriate AVP secretion	7.4%	8.1%	6.8%
Hyperprolactinemia	40.6%	37.5%	41.2%

***Delta height: difference between height at diagnosis and height at last evaluation**

Table III. Clinical characteristics of adult patients at last evaluation

Adult* (N):	male (25)	female (26)
Age (years)	21.2 ± 2.8	19.3 ± 2.6
Weight (kg)	79.4 ± 31.0	64.3 ± 19.1
Weight (SDS)	1.1 ± 4.5	2.1 ± 3.4
Height (m)	1.68 ± 0.08	1.58 ± 0.08
Height (SDS)	-1.1 ± 1.3	-0.7 ± 1.4
Body mass index (kg/m²)	26.0 ± 7.3	24.9 ± 6.2
Body mass index (Z-score)	1.8 ± 1,1	1,7 ± 1,9

***Adult age was defined with an age more than 18 years for males and more than 16 years for females**

A history of central precocious puberty was found in 36% of children. GHD was the most frequent deficiency, with 74% of patients affected, and followed by 57% of thyrotropin deficiency, 36% of corticotrophin deficiency, 33% of hypogonadotropic hypogonadism, 30% of hypergonadotropic hypogonadism, and 15% of central diabetes insipidus. Male and female appeared to be equally affected by endocrine disorder except for hypergonadotropic hypogonadism where male gender is more represented. Endocrine disorders are detailed in Figure 5.

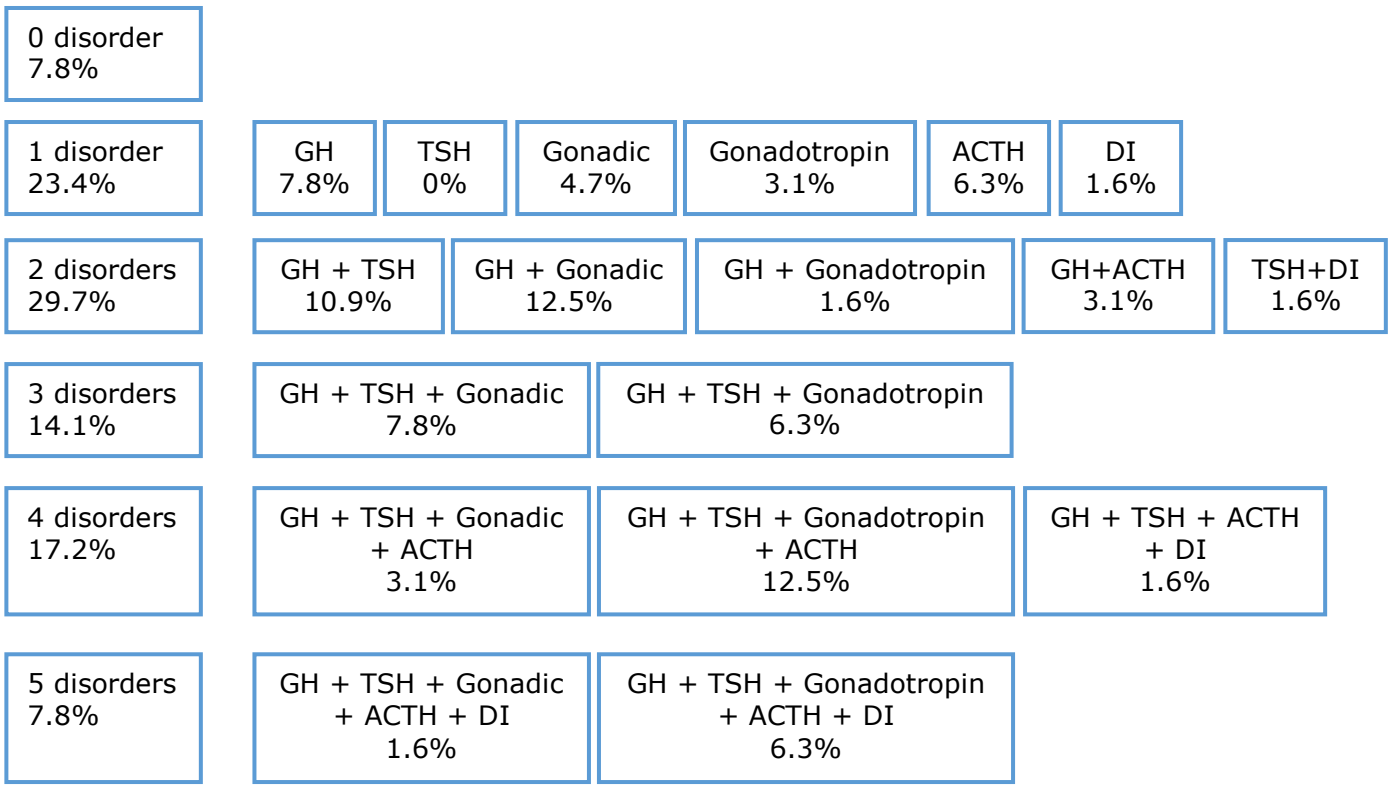


Figure 5: Endocrine disorders at long term evaluation

3.2-Biological characteristics of the patients at last evaluation

Biological characteristics of patients at last evaluation were detailed table IV.

Table IV. Mean biological values of the patients at last evaluation

	all	males < 18 yrs	males ≥ 18 yrs	Females < 16 yrs	females ≥ 16 yrs
N=	**100**	**22**	**26**	**28**	**24**
Mean age [min-max]	**17,3 [9,8-28,1]**	**14,8 [11-17,5]**	**21,3 [18,2-28,1]**	**13,2 [9,8-16]**	**19,9 [16-26,7]**
Sodium (mmol/L)	139 ± 5				
Potassium (mmol/L)	4 ± 0,4				
Chloride (mmol/L)	103,3 ± 5,2				
Bicarbonate (mmol/L)	25,5 ± 3,04				
Calcium (mmol/L)	2,4 ± 0,1				
Phosphorus (mmol/L)	1,3 ± 0,2				
Magnesium (mmol/L)	0,8 ± 0,2				
free T4 (pmol/L)	12,7 ± 3,4				
TSH (mUI/L)	1,8 ± 1,2				
Prolactin (ng/mL)	22,8 ± 20,5				
8 am plasma cortisol (µg/dL)	14,1 ± 8				
ACTH (pg/ml)	30,0 ± 19,6				
DHEA-S (mg/L)		1,8 ± 1,3	2,1 ± 1	1,8 ± 1,1	2,1 ± 2,2
IGF1 (ng/ml)		267 ± 110	200 ± 94	313 ± 130	167 ± 92
IGFBP3 (ng/ml)		3204 ± 1019	3400 ± 1232	3062 ± 1818	3400 ± 1407
FSH (UI/L)		8,7 ± 8,8	15,3 ± 11,1	6,2 ± 6,7	2,7 ± 2,5
LH (UI/L)		3,8 ± 3,8	5,8 ± 3,7	3,7 ± 3,3	2,7 ± 2,9
Testosterone (ng/dl)		432 ± 417	1072 ± 2421		
Estradiol (pg/ml)				45,3 ± 39	56,6 ± 57,4

4-Early predictors of endocrine involvement

Univariate and multivariate regression analyses were shown in Table V.

Table V. Univariate and multivariate regression analyses

	Variables	Univariate analysis OR [95% CI]	p value	Multivariate analysis OR [95% CI]	p value
GHD					
	Age 2,5-4years	0,27 [0,10-0,76]	p=0,01	0.30 [0.10-0.88]	P=0.03
	RT	7,0 [1,51-32,41]	p=0,01		
	Optic nerve location at diagnosis	0,26 [0,09-0,80]	p=0,02		
	CT alone	0.18 [0.06-0.59]	P=0.01	0.19 [0.01-0.65]	P=0.01
Thyrotropin deficiency					
	NF1	0,26 [0,11-0,61]	p=0,00	0.35 [0.14-0.89]	P=0.03
	ICH	3,18 [1,13-8,99]	p=0,03		
	Cachexia	2,92 [0,87-9,78]	p=0,08		
	RT	2,82 [1,14-7,00]	p=0,03		
	Subsequent CT	3,29 [1,41-7,61]	p=0,01		
	Surgery + RT	5,4 [1,46-20,04]	p=0,01		
	Surgery	4,65 [1,68-12,82]	p=0,00		
	BB-SFOP only	0.22 [0.08-0.55]	P=0.00		
	CT alone	0.27 [0.11-0.63]	P=0.00	0.37 [0.15-0.92]	P=0.03
Corticotrophin deficiency					
	NF1	0,16 [0,06-0,46]	p=0,00		
	ICH	3,71 [1,44-9,57]	p=0,01	4,95 [1,64-14.99]	p=0,01
	Age<1year	4,64 [1,63-13,18]	p=0,00	7,47 [2,18-25.65]	p=0,00
	Age 1-2,5years	0,35 [0,12-1,04]	p=0,06		
	Cachexia	4,52 [1,39-14,72]	p=0,01		
	Optic nerve location at the end of BB-SFOP	0,33 [0,10-1,09]	p=0,07		
	Pituitary stalk location at the end of BB-SFOP	3,68 [1,16-11,68]	p=0,03		
	RT	5,03 [2,03-12,44]	p=0,00		
	Procedure(s) for ICH	2,72 [1,13-6,50]	p=0,03		
	Surgery	6,18 [2,39-15,95]	p= 0,00		
	Surgery + RT	14,75 [3,87-59,29]	p=0,00		
	BB-SFOP only	0.25 [0.08-0.72]	p=0,01		
	CT alone	0.19 [0.08-0.47]	p=0,00	0.19 [0.07-0.53]	P=0.00
Hypogonadotropic hypogonadism					
	NF1	0,24 [0,08-0,71]	p=0,01		
	Age<1year	2,81 [0,95-8,32]	p=0,06		
	Pituitary stalk location at diagnosis	4,5 [1,31-15,51]	p=0,02		
	Optic nerve location at diagnosis	0,08 [0,01-0,61]	p=0,02		
	Surgery	5,43 [2,05-14,39]	p=0,00		
	Procedure(s) for ICH	2,45 [0,97-6,2]	p=0,06		
	Surgery + RT	14,46 [4,15-50,47]	p=0,00		

	RT	4,69 [1,81-12,17]	p=0,01		
	Subsequent CT	3,37 [1,25-9,10]	p=0,02		
	BB-SFOP only	0.20 [0.06-0.75]	p=0,02		
	CT alone	0.25 [0.10-0.66]	p=0,01	0.25 [0.10-0.66]	P=0.01
Hypergonadotropic hypogonadism					
	male sex	6,26 [2,06-19,02]	p=0,00	8,41 [2,35-30.12]	p=0,00
	NF1	0,19 [0,07-0,52]	p=0,00	4,85 [1,48-15.95]	p=0,01
	RT	0,21 [0,06-0,70]	p=0,01		
	Numbers of line(s) of CT	0,66 [0,42-1,04]	p=0,08		
	Surgery	0,28 [0,09-0,91]	p=0,04		
	Surgery+RT	0,10 [0,01-0,82]	p=0,03		
	Procedure(s) for ICH	0,26 [0,08-0,85]	p=0,03		
	Optic nerve location at diagnosis	4,1 [1,24-13,60]	p=0,02		
	Optic tracts location at diagnosis	3,36 [0,97-11,66]	p=0,06		
	BB-SFOP only	3.10 [1.12-8.47]	P=0.03		
	CT alone	4.03 [1.46-11.14]	p=0,01	3.12 [1.03-9.46]	P=0.05
Central diabetes insipidus					
	Pituitary stalk location at diagnosis	5,56 [1,33-23,18]	p=0,02		
	Cachexia	6,67 [1,76-25,23]	p=0,01		
	RT	3 [0,90-9,97]	p=0,07		
	Surgery	7,68 [2,10-28,05]	p=0,00	8,56 [2,35-31,2]	p=0,00
	Surgery + RT	8,56 [2,35-31,2]	p=0,00		
Central precocious puberty					
	Age < median	4,18 [1,64-10,66]	p=0,00	2,86 [1,06-7,73]	p=0,04
	Optic tracts location at diagnosis	3,52 [1,14-1,84]	p=0,03		
Obesity					
	Age <1year	2,92 [1,03-8,30]	p=0,04	3,31 [0,95-11,6]	p=0,06
	ICH	4,93 [1,74-13,97]	p=0,00	6,67 [2,09-21,26]	p=0,00
	Pituitary stalk location at diagnosis	4,75 [1,32-17,08]	p=0,02		
	RT	10,74 [4,12-1,58]	p=0,00		
	Surgery + RT	0,04 [0,01-0,95]	p=0,04	6,22 [1,41-27,33]	p=0,02
	BB-SFOP only	0.43 [0.16-1.14]	P=0.09		
	CT alone	0.51 [0.22—1.21]	P=0.13		

OR: Odds ratio, CI: confidence interval

ICH: intracranial hypertension, RT: radiotherapy, CT: chemotherapy

BB-SFOP only regroups patients without subsequent therapy, who received only initial BB-SFOP chemotherapy

Chemotherapy alone regroups patients who received initial BB-SFOP chemotherapy +/- subsequent chemotherapy and no other treatment than chemotherapy

GHD was significantly associated with radiotherapy in univariate analysis and less associated with age between 2,5 and 4 years at diagnosis and chemotherapy alone in univariate and multivariate analysis.

Thyroptropin deficiency was significantly associated with intracranial hypertension at diagnosis, radiotherapy, surgery and radiotherapy and surgery, and less associated with BB-SFOP chemotherapy only, chemotherapy alone and NF1 in univariate analysis. In multivariate analysis, thyroptropin deficiency was significantly less associated with NF1 and chemotherapy alone.

Corticotrophin deficiency was significantly associated with cachexia, radiotherapy, surgery, and procedures for intracranial hypertension in univariate analysis. In multivariate analysis, corticotrophin deficiency was significantly associated with intracranial hypertension and age younger than one year old at diagnosis and less associated with chemotherapy alone.

Hypogonadotropic hypogonadism was significantly associated with radiotherapy and surgery in univariate analysis and less associated with chemotherapy alone, in multivariate analysis.

Hypergonadotropic hypogonadism was significantly associated with male, NF1 and chemotherapy alone in multivariate analysis, and less associated with radiotherapy and surgery in univariate analysis.

Central diabetes insipidus was significantly associated with cachexia, radiotherapy and surgery and radiotherapy, in univariate analysis, and with surgery in multivariate analysis.

Central precocious puberty was significantly associated with younger age at diagnosis (under the median age which was 2.58 years) in multivariate analysis.

Obesity was significantly associated with intracranial hypertension at diagnosis and surgery and radiotherapy, in multivariate analysis and was less associated with chemotherapy alone in univariate analysis.

DISCUSSION

Our main findings were a high rate of endocrine disorder with 94.1% of children with OPG treated with upfront chemotherapy who developed at least one deficiency during follow-up. There was a long period of follow-up in our study (mean time: 13.9 ± 3.7 years). GHD was the most frequent deficiency, with 74% of patients affected, followed by 57% of thyrotropin deficiency, 36% of corticotrophin deficiency, 36% of history of central precocious puberty, 33% of hypogonadotropic hypogonadism, 30% of hypergonadotropic hypogonadism, and 15% of central diabetes insipidus. Multiple pituitary deficiency was the rule with 92% of the patients with two or more deficiencies. Anatomical location on initial MRI was not predictive of late involvement.

Chemotherapy only (either BB-SFOP only or BB-SFOP + subsequent chemotherapy) was protective of late endocrine involvement.

This high incidence of hypopituitarism underscores the need for life-long endocrine follow-up and appropriate replacement.

At last evaluation 46% of patients had obesity (BMI > 2 SDS). We found here that the frequency of obesity increased with time (shown in Annexe III). Late metabolic effects as obesity and its consequences have been well described after childhood cancer therapy. The frequency of obesity varies between 35% to 53%; however studies included several low grade gliomas (LGG), not specifically OPG, and the main treatment were radiotherapy and surgery [15, 22, 31, 51]. It has been showed that tumor location in midbrain/optic nerve was related to earlier weight gain compared with other tumor sites [21]. Intracranial hypertension at diagnosis and subsequent radiotherapy and surgery appeared to be predictors of obesity in our study. To our knowledge, intracranial hypertension at diagnosis has never been described as a predictive factor of long term obesity. Moreover, GH, thyrotropin and corticotrophin deficiencies favor weight gain. Early nutritional care is likely to be of crucial importance to limit later obesity.

Our patients with OPG treated by upfront chemotherapy had reduced adult height at -1.1 SDS in men and -0.7 SDS in women. In our study, 15.4% of women and 20% of men had adult heights two or more standard deviations below population norms which

was quite higher than brain tumor survivors enrolled in Childhood Cancer Survivor Study cohort (with 13% of adult having short stature) [24]. Our patients had -1.75±2.1 SDS mean delta height between diagnosis and last evaluation, this was not described in the hypothalamic/chiasmatic LGG study comparing 2 groups with and without radiotherapy (with respectives mean delta height of -0.36±0.3 and -0.11±0.3 SDS) but the median time of follow-up was 3.6 years, and long term data were lacking [31]. A high rate of GHD (74%) was found in our study, versus 29% to 40% in the literature of childhood brain tumor [20, 22, 31, 52]. These discrepancies may be due to the heterogeneity of type of cranial tumors as well as of treatments reported in the literature. In addition, follow-up was generally shorter in published studies. Chemotherapy has been associated with earlier decrease in IGF1 level (after the mean 20.2 months), and GHD occurred among earliest pituitary deficiencies [21]. Radiotherapy was associated with GHD in our study, which has been well established in literature, and been explained by the fact that GHrH neurons are the most radiosensitive of the axis. However younger age at diagnosis has already been associated with later short stature. This was not the case in our study (GHD was less associated with age between 2.5 and 4 years), likely because the mean age at diagnosis was already young (3.26±0.3 years) and the frequency of GHD was high.

In literature, the occurrence of central precocious puberty was reported in 26% of children with OPG followed up for 8.3 (0.04-26.8) years [22]. In our study, the frequency was higher with 36% of children; this could be explained by the fact that our population was younger at diagnosis and follow-up longer. Thirty eight percent of our central precocious puberty cases occurred among patients with NF1 which is comparable to literature with 39% of children with chiasmal OPG develop precocious puberty [53].

These findings underscored the need to have regular assessments of growth and puberty in those children. Early treatment of precocious puberty may provide additional benefit to adult height. The occurrence of central precocious puberty was not associated with later endocrine involvement in our study and we have not highlighted an association between central precocious puberty and hypergonadotropic hypogonadism as described by others [51].

We found that NF1 status was a protective factor in univariate analysis, whereas intracranial hypertension at diagnosis and cachexia were associated with a higher risk of developing thyrotropin and corticotrophin deficiencies. NF1 has been associated with less aggressive OPG and better overall survival, while intracranial hypertension and cachexia have been associated with a worse prognosis [5, 14, 18]. Up to now, NF1 has not been well established as a protective factor for endocrine involvement [31]. In literature OPG associated with NF1 are considered to have a more indolent course, the radiologic progression, visual deterioration, and endocrine complications were documented more commonly in children with sporadic tumors than in those associated with NF1 [54]. However, the presence of diencephalic syndrome (defined as cachexia) was described to be more predictive of endocrine dysfunction (central precocious puberty and pituitary deficiencies) than treatment related factors such as radiotherapy [31]. In our study, cachexia was significantly associated with central diabetes insipidus, and corticotrophin deficiency in univariate analysis. Otherwise procedures for intracranial hypertension (shunt and/or shunt revision) were significantly associated with hypergonadotropic hypogonadism and corticotrophin deficiency in univariate analysis but not in multivariate analysis. This finding likely suggests watching carefully the children with initial intracranial hypertension, whether requires shunt or not, and cachexia, as they displayed a high risk of long term complication.

Younger age at diagnosis has already been described as a worse prognosis factor in term of overall survival and tumor progression [5, 16]. In our study, we found significant association between younger age and central precocious puberty and corticotrophin deficiency. In a recent study analyzing centrally located low grade glioma (comprising optic pathway glioma) with mostly chemotherapy as initial treatment, a significant association between age and growth hormone deficiency and hypothyroidism has been revealed [40]. This was not the case in our study likely because those deficiencies (GHD and hypothyroidism) had high frequency. This study also showed a strikingly high incidence of neurocognitive abnormalities and endocrinopathies associated with younger age and conclude that efforts to avoid or delay radiotherapy in younger patients still resulted in long term endocrine disorder [40]. This was the case in our study, subsequent radiotherapy was used as salvage therapy, and avoided in young

children (mean age at administration was 9.03 ± 4.01 years) and was still associated with high incidence of late endocrine disorder (GHD, thyrotropin, corticotrophin and gonadotropin deficiencies, and central diabetes insipidus). This confirms the suggestion that even when radiotherapy is delayed with the initial use of chemotherapy in young children, they are still vulnerable to the long-term effects of irradiation [40].

The rates of thyrotropin (57%) and corticotrophin (36%) deficiencies in our study appeared higher than those described in the literature, with respectively 13-33% and 12-26% deficiencies at 15 years of age in the study by Armstrong about low grade cranial glioma (including 7.5% optic glioma among 361 patients)[20][22, 31]. We believe that these discrepancies could be explained by the exclusive report of symptomatic OPG in our study.

When more than one axis was involved, ccorticotrophin deficiency and central diabetes insipidus appeared to be the latest axis affected. We could hypothesize this is due to the localisation of CRH (Cortisol Releasing Hormone) neurones in the paraventricular nucleus which are located the furthest from the chiasma. Moreover, part of AVP secretion (involve in central diabetes insipidus) can occur from paraventricular nucleus.

Percentages of long term hypogonadotropic and hypergonadotropic hypogonadism were respectively 33.3% and 29.8% in our study. Hypogonadotropic hypogonadism has been described in 20-36% of children with low grade glioma in the literature [22, 31]. Hypergonadotropic hypogonadism was less frequently reported in literature. Radiotherapy and surgery applied after BBSFOP chemotherapy was associated with an increased risk of hypogonadotropic hypogonadism, whereas chemotherapy only (either BB-SFOP only or BB-SFOP + subsequent chemotherapy) was associated with an increased risk of hypergonadotropic hypogonadism. This likely reflected a direct effect of radiotherapy and surgery as well as more progressive OPG with direct tumoral effect on the hypothalamic-pituitary area. Surprisingly, subsequent radiotherapy and surgery were apparently protective against hypergonadotropic hypogonadism in our study. This may be due to a protective effect on gonadal function of a silenced gonadotropin function, therefore limiting direct gonadal toxicity of chemotherapy. Alternatively, cranial radiotherapy could only hamper the increase of circulating FSH and LH levels owing to

direct gonadal toxicity of chemotherapy, therefore masking the diagnosis of hypergonadotropic hypogonadism. Further studies will be necessary to assess fertility in these subjects. In addition, fertility preservation might be important to discuss as early as possible in these subjects. Males were more exposed to hypergonadodotopic hypogonadism than females in our study, therefore suggesting that BB-SFOP chemotherapy was more toxic for the testis than the ovary. Carboplatin, cisplatin and cyclophosphamide (included in the BB-SFOP protocol) have been described to cause gonadal failure [26, 27], and chemotherapy-related gonadal toxicity was generally more frequent in males as compared to females [28].

Gan, among others, described hypothalamic involvement as a predictor of earlier endocrinopathies more than treatment [31], this was not the case in our study likely because a high rate (90.4%) of patients had hypothalamic involvement on diagnosis MRI. We did not identify any MRI location in multivariate analysis as predictive factor likely because almost all of our population (97.6%) had chiasmatic and/or hypothalamic involvement. Further studies are necessary to assess location as predictive factors on late endocrine disorders.

Management of symptomatic OPG remains controversial [4, 56, 57]. Numerous studies were concern with overall survival and ophthalmological outcome [5, 58, 59]. Late endocrine sequelae and its consequences, resulting from tumor involvement and/or therapy used (chemotherapy, surgical and/or irradiation treatment), were less described or using small cohort, heterogeneous group of tumor, or follow-up probably not long enough. We described a high rate of late endocrine disorders in this patient, higher than other brain tumor location, and because consequences are not negligible in term of quality of life (obesity, short stature, long life therapies, and psychological repercussions) this endocrine outcomes need to be closely and life-long monitored in this patients, and appropriate replacement treatment should be initiated as earlier as possible. Our main finding was the protective role of chemotherapy only (BB-SFOP only or BB-SFOP + subsequent chemotherapy) on late endocrine involvement, either because reflecting less progressive OPG, or because radiotherapy and/or surgery were not required.

There was limitation in this study that should be acknowledged. The study included only children treated for progressive OPG, and excluded children with asymptomatic OPG that did not justified treatment: we focused on the more severe OPG, hence the high rate of late endocrine dysfunction. A second limitation of this study is the lack of histological diagnosis. Most studies concerning optic pathway glioma have reported a histological diagnosis in a limited number of patients, and the diagnosis was usually established based on MRI, especially for patients with NF1.

In conclusion, obesity and late endocrine dysfunction were frequently found in subjects treated by upfront chemotherapy for OPG during childhood. Chemotherapy when used alone was protective of endocrine sequelae, further underlining that the avoidance of radiotherapy and surgery, if possible, may spare pituitary function.

REFERENCES

1. Bauchet L, Rigau V, Mathieu-Daudé H, et al. Clinical epidemiology for childhood primary central nervous system tumors. J Neurooncol 2009;92(1):87-98.

2. Johnson KJ, Cullen J, Barnholtz-Sloan JS, et al. Childhood Brain Tumor Epidemiology: A Brain Tumor Epidemiology Consortium Review. Cancer Epidemiol Biomarkers Prev. 2014;23:2716–2736.

3. Heideman RL, Freeman CR, Packer RJ, et al. Tumors of the central nervous system. In Pizzo PA and Poplack DG eds. Principles and Practice of Pediatric Oncology, Philadelphia: JB Lippincott 1993;633–681.

4. Dutton JJ. Gliomas of the anterior visual pathway. Surv Ophtalmol 1994; 38(5): 427–452.

5. Rakotonjanahary J, De Carli E, Delion M, et al. Mortality in Children with Optic Pathway Glioma Treated with Up-Front BB-SFOP Chemotherapy. Plos one 2016;10(6):e0127676.

6. Albers AC, Gutmann DH. Gliomas in patients with neurofibromatosis type 1. Expert Rev Neurother 2009; 9(4): 535–539. doi: 10.1586/ern.09.4

7. British Neuro-Oncology Society/NCAT Rare Tumour Guidelines 2011.

8. Singhal S, Kerr B, Birch J, et al. Clinical characteristics of symptomatic sporadic and NF1 related optic gliomata: implications for management. Archives Dis Child 2002; 87:65-70.

9. Hoffman HJ, Humphreys RP, Drake Optic pathways and hypothalamic gliomas: a dilemma in management. Pediatr Neurosurg 1993; 19(4):186-95.

10. Pinson S, Créange A, Barbarot S, et al. Recommendations for the management of NF1. Journal Français d'Ophtalmologie 2002 ; Vol 25, N° 4.pp. 423-433.

11. Gutmann DH, Aylsworth A, Carey JC, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA 1997; 278:51-7.

12. Wolkenstein P, Frèche B, Zeller J, et al. Usefulness of screening investigations in

neurofibromatosis type 1 : a study of 152 patients. Arch Dermatol 1996; 132:1333-6.

13. Allen JC. Initial management of children with hypothalamic and thalamic tumors and the modifying role of neurofibromatosis-1. Pediatr Neurosurg. 2000 Mar;32(3):154-62.

14. Capelli C, Grill J, Raquin M, et al. Long term follow up of 69 patients treated for optic pathway tumours before the chemotherapy era. Arch Dis Child 1998; 79(4): 334–338.

15. Grill J, Couanet D, Cappelli C, et al. Radiation-induced cerebral vasculopathy in children with neurofibromatosis and optic pathway glioma. Ann Neurol 1999 ; 45 : 393-396

16. El Beltagy MA, Reda M, Enayet A. Treatment and Outcome in 65 Children with Optic Pathway Gliomas.World Neurosurg. 2016 May;89:525-34. doi: 10.1016/j.wneu.2016.02.042. Epub 2016 Feb 18.

17. Binning MJ, Liu JK, Kestle JR, et al. Optic pathway gliomas: a review. Neurosurg Focus. 2007;23(5):E2.

18. Laithier V, Grill J, Le Deley MC, et al. Progression-free survival in children with optic pathway tumors: dependence on age and the quality of the response to chemotherapy. Results of the first French prospective study for the French Society of Pediatric Oncology. J Clin Oncol 2003;21(24):4572-4578.

19. Packer RJ, Ater J, Allen J, et al. Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. J Neurosurg. 1997 May;86(5):747-54.

20. Armstrong GT, Conklin HM, Huang S, et al. Survival and long-term health and cognitive outcomes after low-grade glioma. Neuro-Oncology 13(2):223–234, 2011.

21. Ramanauskienė E, Labanauskas L, Verkauskienė R, et al. Early development of endocrine and metabolic consequences after treatment of central nervous system tumors in children. Science direct 2014.

22. Collet-Solberg PF, Sernyak H, Satin-Smith M, et al. Endocrine outcome in long-term survivors of low-grade hypothalamic/chiasmatic glioma. Clin Endocrinol (Oxf) 1997;47(1):79-85.

23. Gurney JG, Kadan-Lottick NS, Packer RJ, et al. Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. Cancer. 2003 Feb 1;97(3):663-73.

24. Diller L, Chow EJ, Gurney JG, et al. Chronic disease in the Childhood Cancer Survivor Study cohort: a review of published findings. J Clin Oncol. 2009 May 10;27(14):2339-55. doi: 10.1200/JCO.2008.21.1953. Epub 2009 Apr 13.

25. Vinchon M, Baroncini M, Leblond P, et al. Morbidity and tumor-related mortality among adult survivors of pediatric brain tumors: a review. Childs Nerv Syst. 2011 May;27(5):697-704. doi: 10.1007/s00381-010-1385-6. Epub 2011 Mar 16.

26. Rose S, Horne V, Howell J, et al. Late endocrine effects of childhood cancer. Nature Reviews Endocrinology 2016;12, 319–336.

27. Nandagopal R, Laverdière C, Mulrooney D, et al. Endocrine late effects of childhood cancer therapy: a report from the Children's Oncology Group. Horm 2008;69, 65–74.

28. Landier W, Bhatia S. Cancer survivorship: a pediatric perspective. Oncologist 2008;13, 1181–1192.

29. Rutter MM, Rose S. Long-term endocrine sequelae of childhood cancer. Curr. Opin. Pediatr 2007;19, 480–487.

30. Shalitin S, Gal M, Goshen Y, Endocrine outcome in long-term survivors of childhood brain tumors. Horm Res Paediatr. 2011;76(2):113-22. doi: 10.1159/000327584. Epub 2011 Jun 17.

31. Gan HG, Phipps K, Aquilina K, et al. Neuroendocrine morbidity after pediatric optic gliomas: a longitudinal analysis of 166 children over 30 years. JCEM 2015.

32. Brauner R, Malandry F, Rappaport R, et al. Growth and endocrine disorders in optic glioma. Eur J Pediatr 1990; 149(12): 825–828. PMID: 2226566.

33. Janss AJ, Grundy R, Cnaan A, et al. Optic pathway and hypothalamic/chiasmatic gliomas in children younger than age 5 years with a 6-year follow-up. Cancer 1995;75(4):1051-1059.

34. Adan L, Trivin C, Sainte-Rose C, et al. GH deficiency caused by cranial irradiation during childhood: factors and markers in young adults. J Clin Endocrinol Metab 2001;86(11):5245-5251.

35. Patterson BC, Wasilewski-Masker K,Ryerson AB,et al. Endocrine health problems detected in 519 patients evaluated in a pediatric cancer survivor program. J. Clin. Endocrinol. Metab 2012;97, 810–818.

36. Dickerman JD. The late effects of childhood cancer therapy. Pediatrics 2007; 119, 554–568.

37. Savage LJ, Murray RD. Late effects of cancer therapy on growth and GH. Int. Growth Monitor 2006;16, 2–7.

38. Schwartz CL, Hobbie WL, Constine LS, et al. Survivors of Childhood and Adolescent Cancer: A Multidisciplinary Approach 3rd ed. Springer-Verlag 2015;1–13; 151–166; 253–281; 339–351; 369–384.

39. Van Dorp W. Long-term endocrine side effects of childhood Hodgkin's lymphoma treatment: a review. Human Reproduction Update 2012;18, 12–28.

40. Terashima K, Chow K, Jones J, et al. Long-term outcome of centrally located low-grade glioma in children. Cancer 2013; 119(14):2630-8. doi: 10.1002/cncr.28110

41. Lambron J, Rakotonjanahary J, Loisel D, et al. Can we improve accuracy and reliability of MRI interpretation in children with optic pathway glioma? Proposal for a reproducible imaging classification. Neuroradiology. 2016 ;58(2):197-208.

42. Sempé M, Pedron G, Roy-Pernot MP. Auxologie, Méthode et Séquences. Paris, Théraplix 1979.

43. Rolland-Cachera MF, Cole TJ, Sempé M, et al. Body mass index variations: centiles from birth to 87 years. Eur J Clin Nutr 1991;45:13–21.

44. Lem AJ, de Rijke YB, van Toor H, et al. Serum thyroid hormone levels in healthy children from birth to adulthood and in short children born small for gestational age. J Clin Endocrinol Metab. 2012 Sep;97(9):3170-8. doi: 10.1210/jc.2012-1759. Epub 2012 Jun 26.

45. Kapelari K, Kirchlechner C, Högler W, et al. Pediatric reference intervals for thyroid hormone levels from birth to adulthood: a retrospective study. BMC Endocr Disord. 2008 Nov 27;8:15. doi: 10.1186/1472-6823-8-15.

46. Soldin SJ, Morales A, Albalos F, et al. Pediatric reference ranges on the Abbott IMx for FSH, LH, prolactin, TSH, T4, T3, free T4, free T3, T-uptake, IgE, and ferritin. Clin Biochem 1995 December 28:603–606

47. Chaler EA, Fiorenzano R, Chilelli C et al.Age-specific thyroid hormone and thyrotropin reference intervals for a pediatric and adolescent population. Clin Chem Lab Med. 2012 Apr 19;50(5):885-90. doi: 10.1515/cclm-2011-0495

48. Nasrallah MP, Arafah BM. The value of dehydroepiandrosterone sulfate measurements in the assessment of adrenal function. J Clin Endocrinol Metab 2003;88:5293–5298.

49. Dodge HW Jr, Love JG, Craig WM, et al. Gliomas of the optic nerves. AMA Arch Neurol Psychiatr 1958 Jun;79(6):607-21.

50. Taylor T, Jaspan T, Milano G, et al. Radiological classification of optic patway gliomas : experience of a modified functional classification system. Br J Radiol. 2008 Oct;81(970):761-6. doi: 10.1259/bjr/65246351.

51. Taylor M, Couto-Silva AC, Adan L, et al. Hypothalamic-pituitary lesions in pediatric patients: endocrine symptoms often precede neuro-ophthalmic presenting symptoms. J Pediatr 2012;161(5):855-63.

52. Grill J, Puget S, De Carli E, et al. Childhood cerebral tumors: morbidity and follow-up into adulthood. Neurochirurgie. 2008 Oct;54(5):623-41. doi: 10.1016/j.neuchi.2008.07.012. Epub 2008 Sep 16.

53. Habiby R, Silverman B, Listernick R, et al. Precocious puberty in children with neurofibromatosis type 1. J Pediatr. 1995 Mar;126(3):364-7

54. Czyzyk E, Jóźwiak S, Roszkowski M, et al. Optic pathway gliomas in children with and without neurofibromatosis 1. J Child Neurol. 2003 Jul;18(7):471-8.

55. Grill J, Laithier V, Rodriguez D, et al. When do children with optic pathway tumours need treatment? An oncological perspective in 106 patients treated in a single centre. Eur J Pediatr. 2000 Sep;159(9):692-6.

56. Listernick R, Darling C, Greenwald M, et al. Optic pathway tumors in children: the effect of neurofibromatosis type 1 on clinical manifestations and natural history. J Pediatr. 1995 Nov;127(5):718-22.

57. Listernick R, Ferner RE, Liu GT, et al. Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. Ann Neurol. 2007 Mar;61(3):189-98.

58. Prada CE, Hufnagel RB, Hummel TR, et al. The Use of Magnetic Resonance Imaging Screening for Optic Pathway Gliomas in Children with Neurofibromatosis Type 1. J Pediatr. 2015 Oct;167(4):851-856.e1. doi: 10.1016/j.jpeds.2015.07.001. Epub 2015 Jul 29.

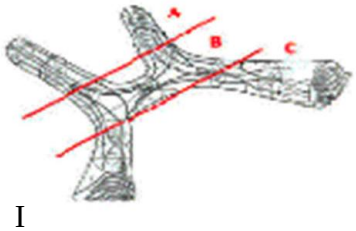
59. Fisher MJ, Loguidice M, Gutmann DH, et al. Visual outcomes in children with neurofibromatosis type 1-associated optic pathway glioma following chemotherapy: a multicenter retrospective analysis. Neuro Oncol. 2012 Jun;14(6):790-7. doi: 10.1093/neuonc/nos076. Epub 2012 Apr 3.

LISTE DES FIGURES

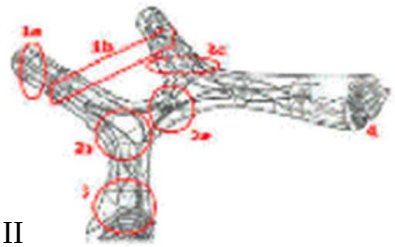
Liste des tableaux

TABLE DES MATIERES

ANNEXE I [41]

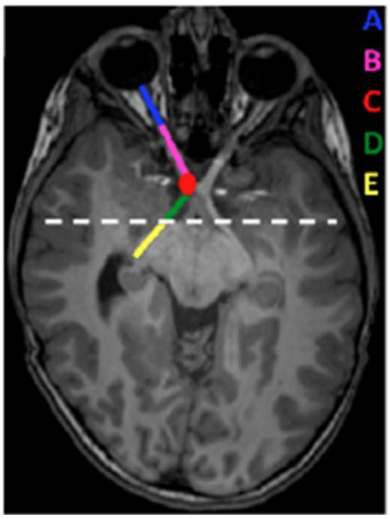


I



II

Optic pathways segmentation according to the Dodge classification (I) (A optic nerve, B chiasm, C optic tracts), the modified Dodge classification (II) (1a single optic nerve, 1b bilateral optic nerve, 1c cisternal segment optic nerve, 2a central chiasmatic, 2b asymmetric chiasmatic, 3 optic tracts, 3b asymmetric tracts, 4 diffuse posterior tracts, 4b asymmetric posterior tracts), and new classification (III) (A optic nerve, B prechiasmatic, C chiasmatic, D retrochiasmatic, E optic tracts and line crossing the anterior part of the cerebral peduncles)



III

Table. QUALITATIVE ANALYSIS. DEFINITIVE INTERPRETATION PROTOCOL

optic nerve [1]	0	1	2	
prechiasmatic [2]	0	1	2	
chiasmatic	0	1		
retrochiasmatic [3]	0	1	2	
optic tracts [4]	0	1	2	
hypothalamic involvement [5]	0	1		
pituitary gland involvement [6]	0	1		
pituitary stalk involvement [7]	0	1		
brainstem involvement [8]	0	1		
forebrain involvement	0	1		
leptomeningeal dissemination [9]	0	1		
ventricular dilatation [10]	0	1		NA
other site of brain disease	0	1		NA

0: absence of involvement / 1: unilateral involvement / 2: bilateral involvement / NA: not applicable.
[1]The optic nerve is limited by the orbital apex. The term refers to the first (intraocular) and second (intraorbital) segments. [2]Prechiasmatic refers to the third (intracanalicular) and fourth (intracranial) segments. [3]The anterior segment of the optic tracts is in front of the anterior portion of the cerebral peduncles. [4]The posterior segment of the optic tracts is behind the anterior part of the cerebral peduncle. [5]Hypothalamic involvement is evaluated on sagittal planes between the pituitary stalk and the mamillary bodies. [6]The pituitary gland is considered as involved when it is thickened, when its limits cannot be observed, or when the sella turcica is involved. [7]The pituitary stalk is considered as involved when it is not observed, when it is thickened or when it is included in the lesion. [8]Including the cerebral peduncles. [9]Meningeal enhancement apart from a postoperative context. [10]When there is no dilatation but a shunt is present, ventricular dilatation is considered as not applicable (NA).

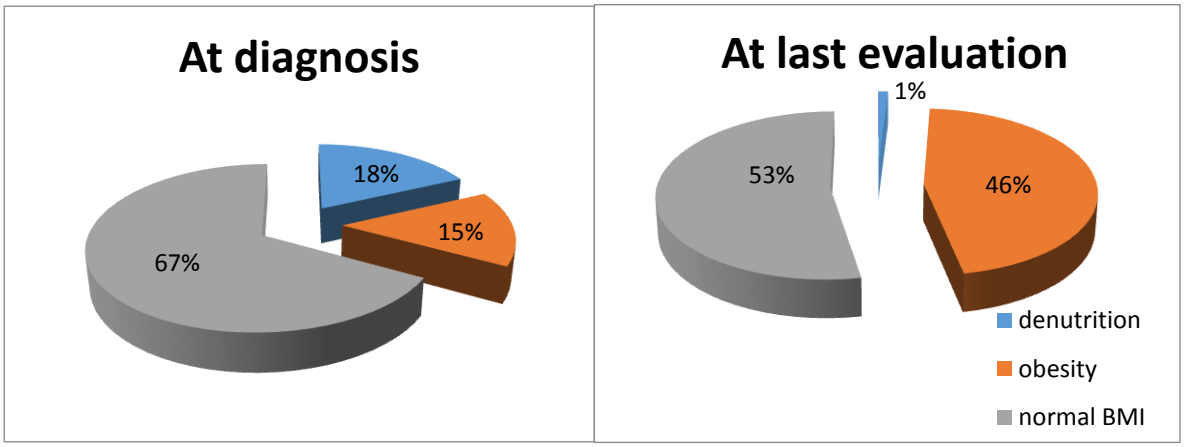
ANNEXE II

Table. Subsequent therapies applied after BB-SFOP chemotherapy

Number of line of subsequent CT	None	One	Two	Three	Four	Five	Six	Seven	Eight	Total
N=	43	27	17	6	4	2	0	2	1	102
Number of patients with subsequent treatment different from CT										
Surgery	2	3	1	0	3	1	0	1	1	12
RT	7	6	1	2	0	0	0	0	0	16
Surgery+RT	3	5	6	3	1	1	0	0	0	19
No specific treatment different from CT	31	13	9	1	0	0	0	1	0	55
Total patient	**43**	**27**	**17**	**6**	**4**	**2**	**0**	**2**	**1**	**102**
Number of patients with surgical procedures for intracranial hypertension										
0 surgical procedure	33	18	11	2	1	0	0	0	1	66
1 surgical procedure	2	2	1	0	1	1	0	1	0	8
2 to 4 surgical procedures	8	6	3	4	2	1	0	1	0	25
>5 surgical procedures	0	1	2	0	0	0	0	0	0	3
Total patient	**43**	**27**	**17**	**6**	**4**	**2**	**0**	**2**	**1**	**102**

ANNEXE III

BMI evolution between diagnosis and last evaluation



HIPPOLYTE Hélène

Atteintes endocriniennes à long terme chez les enfants traités initialement par chimiothérapie de type BB-SFOP pour un gliome des voies optiques et évaluation des facteurs prédictifs de ces atteintes: Etude multicentrique utilisant le protocole national de la Société Française d'Oncologie Pédiatrique (protocole BB-SFOP).

RÉSUMÉ

Introduction. L'attitude thérapeutique actuelle est en faveur de la chimiothérapie comme première ligne de traitement pour les gliomes des voies optiques (GVO) symptomatiques afin de retarder l'utilisation de la radiothérapie et de la chirurgie et d'éviter les séquelles liées à ces traitements. Il existe peu de données sur les atteintes endocriniennes à long terme des GVO traités par chimiothérapie première. **Objectif.** Décrire les atteintes endocriniennes à long terme chez ces patients et identifier des facteurs prédictifs précoces de ces atteintes. **Patients et méthode**. Tous les enfants âgés de moins de 16 ans atteints d'un GVO, traités par chimiothérapie première selon le protocole BB-SFOP en France entre Juin 1990 et Décembre 2004 issu de la base de données BB-SFOP ont été inclus. Le protocole consistait en une polychimiothérapie de 16 mois avec sept cycles de carboplatine, procarbazine, étoposide, cisplatine, vincristine et cyclophosphamide. En cas de tumeur incontrôlée, les enfants ont bénéficié d'un traitement complémentaire (chimiothérapie, chirurgie, radiothérapie). Tous ont fait l'objet d'une évaluation à long terme clinique et biologique (bilan hypophysaire) entre Septembre 2011 et Mars 2016. **Résultats.** Cent deux patients ont été inclus dans notre étude. L'âge moyen au diagnostic était de 3,3 ± 0,3 ans et la durée moyenne de suivi était de 13,9 ± 3,7 ans. A l'évaluation à long terme 36% des patients avaient un antécédent de puberté précoce, 46% présentaient une obésité, 74% présentaient un déficit en hormone de croissance, 57% un déficit thyréotrope, 36% un déficit corticotrope, 33% un hypogonadisme hypogonadotrope, 30% un hypogonadisme hypergonadotrope et 15% un diabète insipide central. Lorsque la chimiothérapie était utilisée seule (sans radiothérapie ni chirurgie), elle était protectrice vis-à-vis des atteintes endocriniennes à long terme. **Conclusion.** L'obésité et les atteintes endocriniennes à long terme ont été fréquemment observées chez les patients traités par chimiothérapie première pour GVO pendant l'enfance. La chimiothérapie, lorsqu'elle était utilisée seule, était protectrice, soulignant en outre le fait que l'éviction de la radiothérapie et de la chirurgie, si possible, peut épargner la fonction hypophysaire.

Mots-clés: gliome des voies optiques, atteintes endocriniennes, chimiothérapie

Long-term endocrine disorders in children treated initially by chemotherapy for optic pathway glioma and evaluation of predictive factors of these sequelae: A multicentric study using the national protocol from the French Society of Pediatric Oncology (BB-SFOP protocol).

ABSTRACT

Background. Therapeutic approach favors chemotherapy as the first-line-treatment in symptomatic Optic Pathway Gliomas (OPG) in order to delay the use of radiotherapy and surgery and decrease the sequelae of such treatments. There are few data on long term endocrine outcomes of OPG treated by upfront chemotherapy. **Objective.** To describe the long-term endocrine disorders in these patients and to identify potential early predictors of the endocrine involvement. **Patients and method.** All the children diagnosed with OPG at an age younger than 16 years, treated with upfront chemotherapy according to the BB-SFOP protocol in France between June 1990 and December 2004, and registered in the French national BB-SFOP registry were included. The protocol consisted of a 16-month polychemotherapy regimen with seven cycles of carboplatin, procarbazine, etoposide, cisplatin, vincristine, and cyclophosphamide. In case of uncontrolled tumor, the children received further treatment (chemotherapy, surgery, radiotherapy). All underwent a late evaluation with clinical and hormonal pituitary assessment between September 2011 and March 2016. **Results.** One hundred and two patients were included in our study. The mean age at diagnosis was 3.3 ±0.3 years and mean time of follow-up was 13.9 ± 3.7 years. At last evaluation, 36% of the patients had a history of precocious puberty, 46% had obesity, 74% had growth hormone deficiency, 57% thyrotropin deficiency, 36% corticotrophin deficiency, 33% hypogonadotropic hypogonadism, 30% hypergonadotropic hypogonadism, and 15% central diabetes insipidus. When chemotherapy was used alone (with no radiotherapy and no surgery), it was protective of late endocrine sequelae. **Conclusion**. Obesity and late endocrine dysfunction were frequently found in subjects treated by upfront chemotherapy for OPG during childhood. Chemotherapy when used alone was protective of endocrine sequelae, further underlining that the avoidance of radiotherapy and surgery, if possible, may spare pituitary function.

Keywords: Optic pathway glioma, endocrine disorders, chemotherapy

université angers UFR SANTÉ