3 Epidemiology, Clinical Presentation, and Prognosis of Adult-Onset Craniopharyngioma

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Abbreviations

AO Adult onset
CO Childhood onset
CP Craniopharyngioma
DI Diabetes insipidus

3.1 History

> "Erdheim Tumor, Hypophyseal Epidermoid Tumor, Rathke's pouch tumor, Rathke cleft cyst or tumor, epithelioma, adamantinoma, ameloblastoma, craniopharyngeal pouch tumors—All craniopharyngiomas": *a long journey*…

The first autopsy description comes from a German pathologist, Friedrich Albert Von Zenker (1825–1898), in 1857 [1]. The autopsy revealed a tumor described as a suprasellar tumor containing cholesterol and a squamous epithelial wall.

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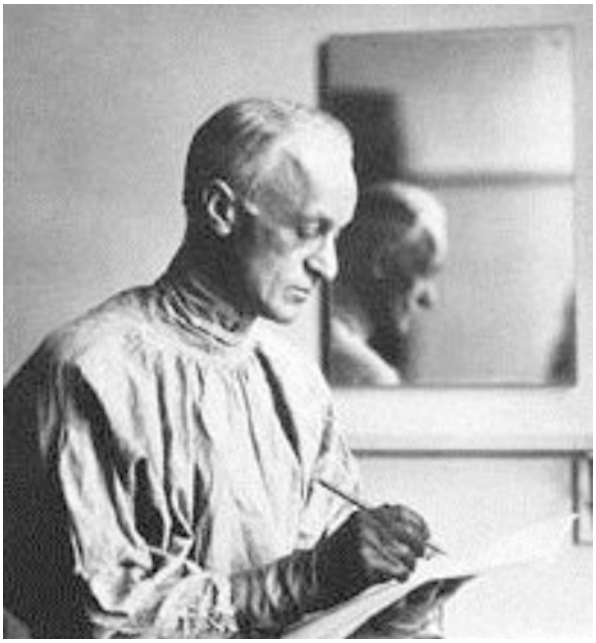
However, to perfectly understand the origin of the tumor, five decades were required. This elucidation of the tumor consisted of several steps: first, with the discovery of squamous cells in the infundibulum of the pituitary gland, by Hubert Von Luschka (1820–1875), that mimic the features of the epithelium of the oral cavity; second, with Martin Rathke (1793–1860), a German anatomist, understanding the role of the evagination of the oral epithelium in the development of the anterior pituitary; thirdly, with Mott and Barret in 1899 followed by J. Erdheim (1874–1937) in 1904, who perfectly described the pathogenesis of craniopharyngiomas (CP).

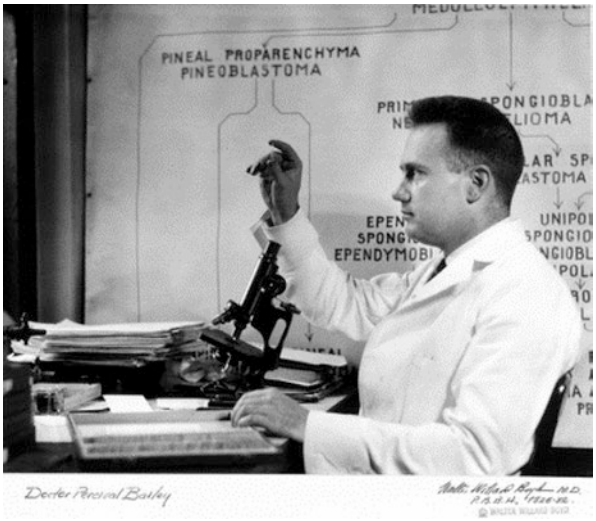
Photograph of Jacob Erdheim, the first to describe the histopathology of craniopharyngiomas

The publication was so impressive that, for decades after, many authors dubbed CP "Erdheim tumors," until CH Frazier, a US surgeon (1870–1936), coined the term CP in 1931, a name that was popularized afterward by H. Cushing, in 1932, in his publication describing more than 2000 cerebral tumors [1].

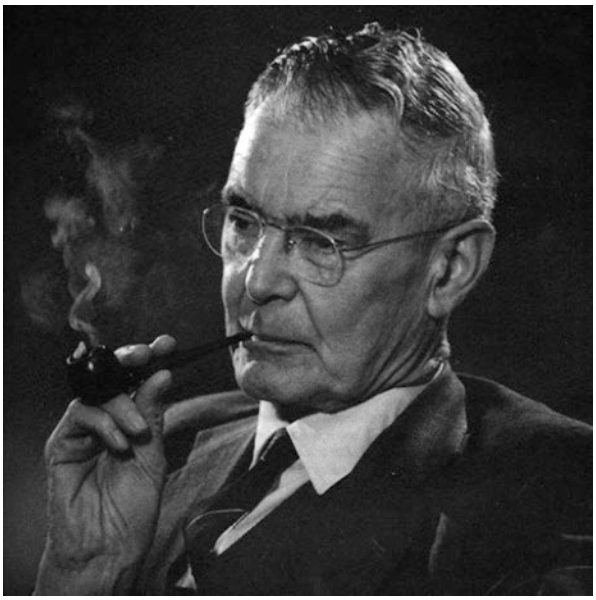


Photograph of Harvey Cushing, the father of modern Neurosurgery, Peter Bent Brigham Hospital, Boston, USA

At the same time, the correlation between the tumor and its clinical presentation was progressively understood. Rupert Boyce and Cecil Beadles in 1893 linked the death of a 35-year-old patient with large suprasellar partially calcified tumors. Mott and Barret in 1893, J. Babinski (1857–1932) and A. Fröhlich (1871–1953), French and Austrian neurologists, respectively, in 1900 and 1901, described the adiposo-genital syndrome termed the Babinski-Fröhlich syndrome. At this point, it was not completely understood which organ was responsible for the symptoms: the pituitary or the hypothalamus. This was the subject of a famous argument between two co-workers: H. Cushing (Neurosurgeon, 1869–1939) and P. Bailey (Neuropathologist and Neurosurgeon, 1892–1973), the latter being opposed to the pituitary being responsible, believing in the role of the hypothalamus. N. Dott (an Irish Neurosurgeon, 1897–1973), and a pupil of H. Cushing, disagreed with his mentor and showed, by his work, the fundamental role of the hypothalamus in controlling, memory, cognition, temperature, feeding behavior as well as endocrine functions.



Photograph of Percival Bailey, neuroanatomist, neurologist, neuropathologist, neurosurgeon, co-worker of H. Cushing for the first human brain tumor classification



Photograph of Norman Dott, Pupil of H. Cushing, Scottish neurosurgeon in Edinburgh

In terms of surgery, the first attempt at removal of a CP (cystic lesion with visual impairment and DI) is attributed to E. Halstead in Chicago, who took a sublabial nasal approach in 1909. For CP, H. Cushing in his own series of 92 CP patients used the nasal route in some, but preferred a sub-frontal approach for a better visualization of the optic structures in most cases. With his skill, the mortality dropped to

15%. His reports mentioned the poor retrochiasmatic exposition and a splitting technique of the optic chiasm to improve tumor exposure. N. Dott contributed to popularization of a two-step technique with firstly a sub-frontal approach and then a secondary transfrontal transventricular approach to reach the ventricular part of the tumor. His surgical description relates in detail how to improve the control of the retrochiasmatic part, sacrificing the blind optic nerve [2]. Using the transventricular route, he therefore perfectly understood the impact that a sharp dissection of the attached tumor may have on the hypothalamus and already advocated for a partial resection. However, surgical results remained poor until the development of antibiotics (Penicillin in 1944) and corticosteroid use (during the 1950s).

Photograph of Gerard Guiot, Pupil of Norman Dott, French neurosurgeon in Paris (Foch Suresnes Hospital) who re-introduced the transsphenoidal route for pituitary tumors

The following decade produced technical refinements with the introduction of the surgical microscope at the end of the 1950s and modern imaging (the CT scan in 1974 and MRI at the beginning of the 1990s). With G. Guiot (1912–1998 [3]), a French neurosurgeon (a pupil of N. Dott) and J. Hardy (1932– [3]), a Canadian Neurosurgeon, a pupil of G. Guiot, the sublabial route was again used for pituitary diseases including CP. In the three last decades, a new surgical tool, the endoscope which allows extended endonasal approaches, has emerged improving the exposure of the tumor especially for the ventricle and retrochiasmatic parts [4, 5]. Italian and US groups, headed by P. Cappabianca and A. Kassam, respectively, greatly contributed to this surgical advance. Nonetheless, regardless of the efforts made during surgery, microscopic tumor removal remains difficult and recurrences frequent.

We are now entering into the promising era of molecular therapy, and thus expect improvements in the management of CP since the results of surgery and radiotherapy approaches have remained sometimes disappointing to date.

Paolo CAPPABIANCA, one of the Pioneers of Endoscopic Endonasal surgery for Pituitary Tumors, Naples, Italy (from left to right; Emmanuel JOUANNEAU, Edward LAWS, Paolo CAPPABIANCA, Engelbert KNOSP)

Amin KASSAM, one of the Pioneers of Endoscopic Endonasal surgery for Pituitary Tumors, starting in the same period as the Naples team, Pittsburgh, Pensylvanny, USA (from left to right: Carl SNYDERMAN, Riccardo CARRAU, Amin KASSAM, Emmanuel JOUANNEAU, Paul GARDNER)

After more than a century of worldwide contributions to treatment, the quote from H. Cushing that "CP are the most formidable of intracranial tumors" still remains perfectly true and CPs continue to challenge neurosurgeons.

3.2 Epidemiology of Adult-Onset CP

Because of the rarity of these tumors, their descriptive epidemiology has been established on scarce studies and remains likely incomplete. Only one publication has analyzed cancer registries including adult patients, collecting exhaustive data in a defined area [6]. In this publication, Bunin and colleagues analyzed data from three US registries : (1) the Central Brain Tumor Registry of the United States (CBTRUS) collected data on CP for the years 1990–1993 from ten state cancer registries representing a total catchment area of 26.8 million US citizens; (2) the Greater Delaware Valley Pediatric Tumor Registry (GDVPTR), a population-based registry of pediatric cancer that covers a region in the eastern USA representing approximately 1.8 million <15 year old children, covering a 30-year period (1970–1989); (3) the University of Southern California/Los Angeles County Cancer Surveillance Program (CSP) has collected data on all new intracranial neoplasms diagnosed in California since 1972, which represents a population of almost 10 million people. Overall, the incidence was 0.5–2.0 cases/million/year. The authors reported no gender or racial difference between Caucasians and African Americans. They noted a bimodal age distribution, classically found in the literature, with the maximum incidence rates in children aged 5–14 years and adults in the sixth decade, giving a calculated incidence of 0.2/100,000/year. In adult-onset craniopharyngioma (AO-CP), the peak incidence was found at 65–74 years in CBTRUS and 50–74 years in Los Angeles county data. The lowest incidence occurred among those aged 15–34 years. In our meta-analysis of the literature regarding AO-CP (see below), we found an average age of 43 years (Table 3.2).

The other published epidemiological study, based on registry data, included only pediatric patients [7].

No environmental risk factor for the development of CP has thus far been identified. However, some studies have shown geographical variations in the incidence of these tumors, suggesting possible involvement of environmental factors [8].

Similarly, no genetic predisposing factor has been identified. Only two reports of siblings with craniopharyngiomas have been published [9, 10].

CP refers to a rare embryonic malformation, probably arising from residual Rathke's pouch cells, developing in the sellar and parasellar region. The adamantinomatous type is the most frequent histological diagnosis, even in AO-CP. Squamous papillary tumors are more commonly found in AO-CP than in childhood-onset craniopharyngioma (CO-CP) [11, 12], and represent 25.9% of the AO-CP cases (Table 3.2). Malignant transformation (MT) remains extremely rare, with a recent review finding only 23 reported cases [13]. Squamous cell carcinoma represented the most frequent type (80.96%). The authors reported a median time from initial

benign diagnosis to MT was 8.5 years (range, 3–55 years). The median overall survival after MT was 6 months (range, 2 weeks to 5 years).

3.3 Clinical Presentation of Adult-Onset Craniopharyngioma

Morbidity associated with CP is related to tumoral development along the hypothalamo-hypophyseal tract and its proximity to important anatomical features, in particular the opto-chiasmatic and hypothalamic structures.

3.3.1 Our series (Table 3.1)

We recently reviewed the last pure adult-onset CP cases that were newly diagnosed in the department and operated on using an endonasal approach during the last 6 years. To give a clear picture of the initial clinical presentation, we have excluded patients here that were referred or followed-up patients that had been previously treated.

The population is composed of 22 patients (from 51 AO-CP patients in all treated during the same period) with a majority of females (sex ratio F/M = 2.14). The mean age was 58 years (range 18–79) (see Table 3.1).

3.3.1.1 Ophthalmology

Visual impairment was the main complaint in 65% of the population (association of visual acuity and visual field impairment in almost all cases) and only 30% of patients had a normal visual examination.

3.3.1.2 Endocrine Symptoms

Fifty five percent of patients had normal endocrine status, whereas 27% had panhypopituitarism, 18.2% isolated hypogonadism, and 13.6% had diabetes insipidus (DI).

3.3.1.3 Non-specific Symptoms

Surprisingly, headaches were reported by only 9% of our patients in this series. An obstructive hydrocephalus occurred in 9% of patients, requiring immediate CSF shunt.

3.3.1.4 Hypothalamic and Limbic Symptoms

Weight issues were classified as follows: normal when BMI was between 18.5 and 24.9, overweight between 25 and 29.9, obese when greater than 30 (class I: 30–34.9; class II: 35–39.9, and class III: morbid obesity over 40) (World Health Classification).

Interestingly, unexplained weight issues occurring recently prior to diagnosis were frequently reported in our population. At diagnosis, 73% of the patients were overweight with obesity seen in 37% (class I: 23%; class II: 14%). Only 27% were

Table 3.1 Pre-operative

Parameter		Our series (n = 22)	
Population		n	%
Sex	Male	7	30
	Female	15	70
Age (years), median		58 (18–79)	
Pre-operative characteristics			
Visual status (n = 20)	Normal	6	30
	Visual field abnormalities	11	55
	Unilateral decreased visual acuity	7	35
	Bilateral decreased visual acuity	5	23
	Visual impairment as main complaint	13	65
Endocrine status	Normal	12	55
	Panhypopituitarism	6	27
	Isolated hypogonadism	2	9
	Isolated hyperprolactinemy	2	9
	Diabetes insipidus	4	18
Neurological status	Vertigo	1	5
	Signs of elevated intracranial pressure	2	9
	Headaches	2	9
Cognitive status	Cognitive impairment	5	23
	Slow-down or signs of depression	4	18
Social status	Working	11	50
	Retired	8	36
	Work stoppage	3	14
Weight	BMI <25	6	27
	BMI [25; 30]	8	36
	BMI [30; 35]	5	23
	BMI >35	3	14
Height	Female	161 ± 3	
	Male	176 ± 5	
MRI grading	Grade 0	1	4
	Grade 1	7	32
	Grade 2	14	64

normal weight. The recent occurrence of overweight before diagnosis represented strong evidence of disease-related symptoms. Not surprisingly, statistics was difficult on such a small cohort, with grade 2 of the Puget MRI classification (tumor involving the third ventricle floor) being correlated with overweight except in the case of two grade two patients with normal body weight.

In our retrospective review, pre-operative neuropsychological tests were not performed but clear cognitive dysfunction or depression was noted in, respectively, 23 and 18% of patients without any cause, except in one case who had a prior history of depression. Among the 14 active patients, 3 had stopped work because of a cognitive impact. Once again, these symptoms were related to hypothalamic involvement.

3.3.1.5 Radiology and Histology

In terms of tumor types, using the PUGET classification [14], we found 1 grade 0, 7 grade 1, and 14 grade 2 tumors. Most of the adult tumors were suprasellar-secondary intraventricular and infundibulotuberal tumors and were rarely purely intraventricular or sellar type. We found more adamantinomatous (75%) than papillary tumors (25%).

3.3.2 Literature

A recent meta-analysis of AO-CP management has been published [15]. However, this publication included only a few series with mixed populations of AO-CP and CO-CP patients in which individual data on AO-CP could not be extracted, as well as papers that were quite old.

To avoid these biases, we proceeded to perform a similar literature review using Medline and Embase databases, to analyze epidemiology and clinical presentation of AO-CP, including recent series reporting individual data on AO-CP patients, published in the last 20 years, and excluding all articles with undifferentiated mixed populations of CO-CP and AO-CP or populations of CO-CP. We aggregated the results of our series of 22 patients with data from 15 AO-CP studies, representing a total of 709 patients, comprised of 56.1% of males, with a mean age of 42.7 years. Details of this analysis are shown in Table 3.2.

3.3.2.1 Ophthalmology

As is the case in CO-CP, visual disorders represent the most common findings in AO-CP. Visual field impairment is found in 60–85% and visual acuity impairment in 40–74% [30, 31]. In our meta-analysis, we found an overall rate of 68.9% of visual defects (Table 3.2). Some authors reported higher percentages of visual impairment in AO-CP than CO-CP (85% vs 59%) [31] while others did not [30, 32]. Blindness remains rare (3% of AO-CP), whereas optic atrophy affects 15% of patients [30].

3.3.2.2 Endocrine

At clinical presentation of AO-CP, symptoms of pituitary failure are frequent: half of the patients have at least one endocrine manifestation [32]. Most of the time, patients present partial deficiencies (73%); galactorrhea was found in 8% of patients at the time of diagnosis of AO-CP, impaired sexual function in 28%, and menstrual disorders in 57% of female patients [30]. Complete anterior panhypopituitarism at diagnosis has been reported in only 12% of AO-CP, complete panhypopituitarism was found in only 3%, and ADH deficiency in 6% of AO-CP [31]. In our meta-analysis, we found an overall rate of 29.9% of anterior pituitary failure (partial or complete) and 17.9% of diabetes insipidus (Table 3.2). Endocrine dysfunction appears to be more frequent in children [29].

3.3.2.3 Hypothalamic and Limbic Symptoms

In addition to the resulting pituitary dysregulation, hypothalamic impairment can lead to dysfunction of feeding and drinking, arousal (wakefulness and attention),

Table 3.2 Epidemiology and clinical presentation in series including individual data on patients with AO-CP

Series	*N*	Average age	Male sex%	Histo: papillary%	Visual impairment	Anterior pituitary impairement	DI	Hypothalamic impairment	Headache	Hydro
Balde et al. [16]	35	44.7	75	NA	37.1	37.1	5.7	5.7	31.4	NA
Bosnjak et al. [17]	8	63	50	NA	87.5	12.5	0	NA	NA	12.5
Dandurand et al. [15]	22	46.7	55	45.4	95.6	22.7[a]	NA	4.5	36.4[b]	NA
Eldevik et al. [18]	24	38.5	41.7	33.3	NA	NA	NA	NA	NA	NA
Frank et al. [19]	9	44.9	44.4	NA	77.8	88.9	0	NA	NA	NA
Gardner et al. [20]	16	54.9	62.5	NA	87.5	37.5	12.5	NA	NA	NA
Jung et al. [21]	41	45.8	57.8	26.8	63.8	26	10.9	NA	24.4	0
Kim et al. [22]	16	40	75	NA	100	100	56.3	NA	NA	NA
Kim et al. [23]	146	41.4	59.6	34.9	66.4	51.4[a]	NA	NA	52	19.2
Lee et al. [24]	90	43.3	55.5	NA	66.7	5.5	26.7	NA	50	NA
Lee et al. [25]	82	42	64.3	23.5	78.1	11	12.2	19.5	40.2	NA
Leng et al. [26]	21	48.3	38	17.6	81	66.7	23.8	NA	14.3	4.2
Lopez-Serna [27]	153	32.4	51.6	16.3	66.7	70.5[a]	NA	NA	11.7[c]	NA
Norris et al. [28]	8	29	62.5	NA	50	87.5	25	NA	50	12.5
Wang et al. [29]	16	32.2	43.8	18.2	NA	75	18.8	NA	50	NA
Our series	22	58	31.8	23.8	70	45.2	18	73	9	9
Overall	709	42.7	56.1	25.9	68.9	29.9	17.9	21.7	42.3	13.4

[a]Unspecified endocrinopathies (mixed anterior and posterior pituitary failure)
[b]Headache + hydrocephalus
[c]Headache + intracranial hypertension syndrome

energy balance, memory, circadian rhythm, panting, sweating, and autonomic nervous system regulation (blood pressure, heart rate, and gastro-intestinal tract stimulation).

Our own series provides evidence of frequent hypothalamic signs (weight issues in 73% and cognitive impairment in 41%). In our meta-analysis, the percentages are clearly lower, with an overall rate of 21.7% with hypothalamic dysfunction (Table 3.2).

Overweight and obesity represent the more common findings in hypothalamic damage. Disruption of responses to leptin and insulin within the hypothalamic arcuate nucleus (located in the median eminence), responsible for controlling satiety, hunger, and regulating energy balance, results in hyperphagia, autonomic imbalance, reduction of energy expenditure, and hyperinsulinemia [33]. In these patients, obesity may also be influenced by behavioral disorders, mood alterations, and increased anxiety-related personality traits [34]. The weight gain is generally refractory to usual dietary or lifestyle interventions and to pharmacotherapy. Bariatric surgery has been proposed as a treatment alternative but its effectiveness remains uncertain [35]. Prevalence of obesity in AO-CP is unequivocal. In a large series that differentiated CO-CP (n = 112) and AO-CP (n = 112) [31], authors found significantly less obesity in AO-CP than in CO-CP. Only 16% were obese at diagnosis (Class I obesity (30 < BMI < 35): 10%; Class II obesity (35 < BMI < 40): 4%; Class III obesity (BMI ≥ 40.0): 2%), 39% were overweight but not obese, and 41% had normal weight. In contrast, in another large series, overweight and obesity were more prevalent in AO-CP (52%) compared with CO-CP patients (40%)[36]. In our series, we also found significantly more overweight and obese patients. Compulsive behavior seemed, however, to be less frequent. Thus, AO-CP series are probably not large enough to draw definitive conclusions.

The opposite situation, of anorexia/weight loss, is rarely seen affecting only 2–8% of AO-CP patients [30, 31].

Surprisingly, hypothalamic data on AO-CP are scarce in the literature, especially regarding cognitive functions.

3.3.2.4 Other Symptoms

Headache is a common symptom at diagnosis of CP, reported in up to 56–65% of adult-onset CP patients [30–32]. These are most of the time non-specific; intracranial hypertension has been described in only 15% of AO-CP [32]. Only one study found significantly less headaches in adult-onset CP than in childhood onset CP (56 vs 78%) [30]. In our meta-analysis, we found an overall rate of 42.3% with headache at presentation (Table 3.2), while in our series, the frequency of headaches is low and related to hydrocephalus.

Hydrocephalus is significantly less common in patients with AO-CP than CO-CP (18% vs 40%) [31]. Tumoral resection can be sufficient to restore functional CSF flow; however, CSF shunting is often necessary. In our meta-analysis, we found an overall rate of hydrocephalus at diagnosis of 13.4% (Table 3.2).

Other findings such as neurological deficits or an altered level of consciousness remain very unusual at clinical presentation but are probably underestimated because of a small cohort in which that aspect was not really addressed.

3.4 Long-Term Morbidity and Mortality in Treated Adult-Onset CP

The long-term morbidity and mortality in CP is dependent on intrinsic factors (related to the tumor characteristics) and extrinsic factors (related to treatment modalities). Morbidity includes hypopituitarism, hypothalamic impairment, visual, neurological, and cognitive deficits, as well as increased cardiovascular risk and reduced bone health, resulting in a significant reduction in quality of life (QoL) [37].

3.4.1 Morbidity

Management of CP must be directed by therapeutic outcomes rather than surgical parameters. *Optimal surgical management of AO-CP remains controversial.* In particular, it is still unclear if GTR is better than STR associated with radiotherapy. In their meta-analysis, Dandurand et al. found a recurrence rate that was slightly lower in gross total resection (GTR) than in subtotal resection (STR) completed by radiotherapy (RXT), though this did not reach significance (OR: 0.63, 95% CI: 0.33–1.24, $p = 0.18$) [9]. Thus, the aggressiveness of surgical resection should be adapted from case to case, taking into account the balance between risk of recurrence and risk of post-operative sequelae. The impact of the surgical route (endonasal or cranial approach) on long-term prognosis has never been precisely reported although some authors [38] have shown better results with the ventral approach than with the cranial route. There should be, therefore, no dogma in the field and the choice should aim for the shortest direct route and adequate exposure of the tumor interface and critical structures [39]. Lastly, surgery for recurrence is associated with higher morbidity and mortality [9].

3.4.1.1 Endocrine Morbidity

The surgical management of the pituitary stalk that influences endocrine outcome remains uncertain. Post-operative hypopituitarism is consistent and complete when the stalk is resected during surgery. Some authors suggest that in about 50% of cases, the stalk is not invaded by the tumor and thus recommend its anatomical preservation: in a retrospective study of 122 surgical cases (mixture of children and adult patients), Van Effenterre et al. reported a surgically preserved stalk in 54 patients using a cranial microscopic approach; at 1 year follow-up, 30% of them had a panhypopituitarism, 33% had a partial deficiency, and 37% had intact pituitary function (30% had total tumor removal

and 7% had partial tumor removal) [40]. However, other authors have suggested that preserving the pituitary stalk does not guarantee intact endocrinological functions post-operatively, and the surgical strategy should focus on the quality of the resection (GTR) in order to avoid a tumor remnant [41]. Thus in another study, stalk preservation was achieved in 24 patients out of 39 (61.5%); post-operatively 14 (58.3%) had a persistent complete pituitary insufficiency, 2 (8.3%) had incomplete pituitary insufficiency, and 8 (33.3%) had preserved pituitary function [13]. In this series, the rate of recurrence was similar in patients who had stalk preservation (25%) and in patients who underwent stalk section (26.7%). Finally, the possibility of preserving the pituitary is related to the origin of the tumor (sellar, suprasellar secondary intraventricular, intraventricular tumors where preservation can be tried, and infundibulotuberal tumors where is no possibility of preservation) and to the experience of the surgeon as well. In a more simple way, preserving the stalk does not override tumor treatment, even if we know the endocrine outcome is likely worse.

Long-term endocrine morbidity remains definitely high. In recent publications, the prevalence of complete anterior pituitary insufficiency was reported to be as high as 89 % [10], with specific TSH, GH, ACTH, gonadotropin insufficiencies, and DI in 86%, 91%, 92% 93.5%, and 81% of cases, respectively [42]. Hypopituitarism, by itself, has been reported to impact QoL [43] and is associated with an overall excess mortality, with a standardized mortality ratio (SMR) of 1.55 [44]. This excess mortality particularly affects women and young patients.

3.4.1.2 Ophthalmologic Morbidity

Visual impairment in AO-CP was reported to be as high as 40–47% at 10 years follow-up [30, 45], and visual field impairment up to 63% [46]. However, endonasal surgery may have a better visual outcome than cranial surgery and, in our own experience, the visual results were good in more than 90% of patients, who were able to resume normal activities.

3.4.1.3 Hypothalamic Morbidity

Overall, the high morbidity and poor prognosis associated with CP significantly reduce the quality of life (QoL) of patients. As previously mentioned, the primary sequelae affecting patients' QoL are visual impairment and endocrine deficits but hypothalamic lesions also caused overweight issues, neuropsychological deficits, and emotional instability [37]. Quite surprisingly, few data have been reported showing hypothalamic outcomes in AO-CP to date. This reduction in QoL has been found to be more pronounced in AO-CP than in CO-CP, with no gender difference [36]. In the AO-CP group, authors reported a strong correlation between BMI and QoL reduction. Our own data has shown, however, that almost all patients, with the exception of 2, resumed normal daily activities or work at the same level despite overweight issues after surgery. Cognitive functions have been significantly improved as well. This highlights that further studies are warranted for AO-CP in large prospective series.

Post-operative hypothalamic morbidity is also correlated with the severity of adhesions which can be evaluated pre-operatively on MRI [47]. Readers should refer to

the specific chapter in this book by Prieto et al. Adamantinomatous subtypes would be more infiltrative, limiting the possibility of achieving GTR, whereas papillary subtypes may have a better outcome and fewer cases of recurrence [48].

3.4.2 Mortality

Craniopharyngioma accounts for the highest mortality of all tumors arising from the sellar region, with women more affected than men [49, 50]. The standardized morbidity ratio (SMR) was reported to be as high as 19.4 [50].

The overall survival rates in recent publications are reported as between 89 and 94% at 5 years, 85 and 90% at 10 years, and 62 and 76% at 20 years [30, 40, 42, 51].

Female sex, hydrocephalus, hypothalamic damage, incomplete tumor resection, tumor recurrence, repeated surgery, radiotherapy, panhypopituitarism, and obesity were found to be risk factors for excess mortality [30, 31, 42, 45, 49].

This mortality is highly dependent on the age at diagnosis: survival being better among children than AO-CP patients. In the US national cancer database analysis, 5-year survival rates were reported to be 99%, 80%, and 38% when diagnosis was made in patients who were aged <20 years, 20–64 years, and >65, respectively [6]. In a large national population-based study [52] the reported 5-, 10-, and 15-year survival rates were lower for AO-CP (86%, 82%, and 64%, respectively) in comparison to CO-CP (100%, 96%, and 89%). In this study, authors found an average of 9.6 years of life lost in patients with AO-CP.

Endocrine impairments have a negative impact on mortality: patients without hormonal deficiency have only 2.3 years of life lost compared with patients with hypopituitarism and/or DI who lost 18.5 years of life [52].

Several studies showed higher mortality for women compared to men [30, 31, 42, 45, 49], possibly resulting from the fact that women with hypopituitarism not only have unsubstituted hypogonadism but may also have an unfortunate exposure to the combinations of estrogens and progestogens.

Long-term overall vascular morbidity has been found to be significantly higher in CP patients in comparison with the general population (22% vs 4.8–8%), with 16% incidence of cerebrovascular accidents and 6% of myocardial infarctions, compared with 1–3.2% and 3.8–4.8%, respectively, in the general population [45]. Patients with CP have a 3–19-fold higher cardiovascular mortality in comparison to the general population [45, 49, 50]. Female gender, in particular premenopausal estrogen-deficient patients, appears to be significantly more affected than men by cardiovascular morbidity and mortality (SMR is twofold higher in females) [45, 49].

The literature does not provide robust data to determine the potential contribution of tumor size, tumor site, or surgical approach on mortality in patients with CP [53].

Post-operative mortality ranges from 0 to 16.9% [40] in cases of primary surgery and up to 10.5–40.6% in procedures on recurrent tumors [54, 55]. Our own experience demonstrated that in older patients with severe pre-operative morbidity factors (mainly cardiovascular morbidity associated with severe obesity), the rate of mortality is very high bringing into question a palliative approach rather than a curative one.

3.5 Modern Management of CP Improves Prognosis?

The introduction of MRI in the 1990s has undoubtedly transformed the management of CP. Precise evaluation of tumor size, location, and extent allows for a good evaluation of the expected difficulties and probability of successful radical surgical excision. In particular, MRI evaluation of the potential tumoral adhesions (in particular, invasion of the hypothalamus and anatomical situation of the optic chiasm) could help to confirm the most feasible surgical route and anticipate the individual surgical risks [47].

Progress in diagnosis and management of CP has resulted in a significant improvement of prognosis. In a population-based study (period 1951–1982, Finland), the analysis of 5-year survival rate after diagnosis for patients diagnosed in the 1970s, 1980s, and 1990s was reported as 73%, 91%, and 98%, respectively [56]. However, interpretation of these findings must be nuanced. For example, in a comparison of patients treated before or after 1987 for CP, Olsson et al. found no difference in prevalence of myocardial or cerebral infarctions among CP patients.

3.6 Conclusion

In summary, AO-CP are rare sellar/suprasellar tumors (accounting for 4% of our adult pituitary cases per year). Their management and prognosis slightly differ from CO-CP with more sellar-suprasellar tumors, accessible by endonasal extended transtubercular approaches. At the time of diagnosis, endocrine, visual, and/or cognitive morbidity is present in more than two thirds of cases. The literature provides only poor data on hypothalamic dysfunction and alteration of quality of life in AO-CP patients, pre- and post-operatively, and further studies are therefore warranted. The long-term morbidity remains high, depending on the tumor characteristics and treatment modalities. However, our own data seems to indicate that despite hypothalamic issues, social integration of patients may be better than that of children. The mortality related to AO-CP is higher than in CO-CP, in particular in young patients and women, and remains a concern for surgery in obese patients with negative prognostic factors and repeat surgery.

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