Harvey Cushing's craniopharyngioma treatment: Part 1. Identification and clinicopathological characterization of this challenging pituitary tumor

*José María Pascual, MD, PhD,¹ Ruth Prieto, MD, PhD,² and Laura Barrios, BS³

¹Department of Neurosurgery, La Princesa University Hospital; ²Department of Neurosurgery, Puerta de Hierro University Hospital; and ³Statistics Department, Computing Center, CSIC, Madrid, Spain

OBJECTIVE Harvey Cushing (1869–1939) coined the term “craniopharyngioma” (CP) in 1929 to describe a kaleidoscopic group of epithelial tumors involving the hypothalamic-pituitary axis. Throughout his career, he endured a long struggle to accurately diagnose and safely remove these complex lesions, and his resulting surgical series has never before been analyzed in depth. The authors here conduct such an analysis.

METHODS In this study, the authors retrospectively examined the CP patient records available in the Cushing Brain Tumor Registry, as well as those CP cases reported by Cushing in medical monographs and scientific reports.

RESULTS Cushing's CP series comprises a total of 124 tumors (CP₁₂₄) compatible with a CP diagnosis. Among this series are 92 cases that could be pathologically verified (CP₉₂). This subcohort showed a bimodal age distribution (41% aged ≤ 19 years old) and a balanced sex distribution. Clinical evolution up to diagnosis was longer than 3 years in half of the patients. Typical symptoms found at diagnosis were severe headache (94%), visual deficits (97%), panhypopituitarism (76%), psychiatric disturbances (47%), and abnormal somnolence (47%). The highest rate of endocrine deficits occurred in patients younger than 19 years of age ($p < 0.001$), whereas hypothalamic disturbances were observed mainly in adults between 30 and 49 years ($p = 0.02$). Hydrocephalus was present in 63% of the patients, predominantly involving the younger subgroup ($p < 0.001$). Preoperative diagnosis was based on clinical signs, fundoscopic exams, and skull radiographs, the latter study showing suprasellar calcifications in 64% of cases. The majority of tumors (61%) had developed within the third ventricle (3V) or had invaded it. The adamantinomatous histological variant was the predominant one (73%). Squamous-papillary CPs occurred only in adults older than 40 years of age ($p < 0.001$). Strong CP adherences to the hypothalamus were demonstrated in 63% of cases. The infundibulo-tuberal and sellar/suprasellar–3V CP topographies were associated with the highest rates of hypothalamic dysfunction before surgery ($p < 0.001$), surgical hypothalamic injury ($p < 0.001$), and severe postoperative morbidity and/or mortality ($p = 0.009$). Both topographies showed the strongest adherences to the hypothalamus and 3V ($p < 0.001$).

CONCLUSIONS Cushing's CP series comprises severely ill patients with tumors in the late stages of progression, with a high rate of tumors developing primarily within the hypothalamus (infundibulo-tuberal CPs) or invading this structure from the sellar/suprasellar regions. Craniopharyngioma topography was the fundamental variable influencing the clinical manifestations, tumor features, and patient outcomes in this series.

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KEYWORDS craniopharyngioma; Harvey Cushing; history of pituitary surgery; hypothalamus; infundibulum; third ventricle; pituitary tumors; pituitary gland

Since scarcely any two are precisely alike and since those of similar size and character show such differences in behavior, the course of any given tumor is impossible to foretell.

— *Harvey Cushing, 1932*¹¹

Harvey Williams Cushing (1869–1939) is considered one of the founding fathers of neurosurgery (Fig. 1A).⁸ He laid the foundations for the surgical treatment of most intracranial tumors with his groundbreaking monographs on

ABBREVIATIONS BTR = Brain Tumor Registry; CP = craniopharyngioma; CP₉₂ = Cushing's subcohort of 92 pathologically verified CPs; CP₁₂₄ = Cushing's entire series of 124 CPs; DI = diabetes insipidus; IT = infundibulo-tuberal; 3V = third ventricle; 3VF = 3V floor.

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* J.M.P. and R.P. contributed equally to this work.

FIG. 1. A: Portrait of Harvey Williams Cushing (1869–1939), artist William James, 19th–20th century, oil on canvas, sight: 75.7 × 50.4 cm, framed: 90.5 × 65.4 × 3.8 cm, Harvard University Portrait Collection, gift of the three daughters of Harvey Williams Cushing to the Medical School, 1948, HNA72. It is hung at Harvard's Countway Library of Medicine, Boston, Massachusetts. Photograph Imaging Department © President and Fellows of Harvard College. Reprinted with the kind permission of the Harvard Art Museums. **B:** Drawing of an interpeduncular cyst, sketched by Harvey Cushing at the time of autopsy. It corresponds to the first intracranial tumor (case 1) surgically treated by Cushing, February 1902, at Johns Hopkins Hospital. Although this lesion was considered a “teratoma” by William Welch (1850–1934), head of the Hopkins Pathology Department at the time, multiple sources of evidence indicate that this tumor actually corresponds to a CP. From Cushing: *J Nerv Ment Dis* 33:704–716, 1906. Public domain. **C:** Pictures of a patient (case 110) taken on July 26, 1929, and a discharge note showing Cushing's handwritten word “craniopharyngioma,” its first appearance in his BTR. From Cushing's BTR. Public domain. Panels B and C courtesy of the Manuscripts and Archives department of the Sterling Memorial Library, Yale University. Figure is available in color online only.

pituitary adenomas, acoustic schwannomas, gliomas, and meningiomas.^{5,14,17,19} Above all these tumors, however, was a seemingly benign type of suprasellar lesion that puzzled Cushing and over which he obsessed throughout his career, as it very often proved intractable (Fig. 1B).³¹ Cushing himself coined the term by which this tumor type is universally known today: “craniopharyngioma” (CP; Fig. 1C).^{27,34}

Cushing failed to publish a complete, in-depth review of his pioneering 30-year surgical experience with CPs, the first large series of these complex tumors in the history of medicine. This is particularly regrettable as there are many valuable lessons to be learned from his observations on CPs, which remain a major neurosurgical challenge. From his statements, we know that he aimed to publish his series as, in 1929, he had commissioned the task of reviewing all of his material to his Dutch trainee, Ignace Oljenick.^{9,27} In the end, Oljenick was unable to accomplish the project. For this reason, Cushing only prepared a brief report on his extensive, unparalleled surgical knowledge of CPs in a chapter included in his monograph *Intracranial Tumors*, published in 1932, the same year as his retirement.¹¹ A complete account of Cushing's CP series has never been produced.

Providentially, Harvey Cushing painstakingly recorded, documented, and maintained every patient's history, including the tumor tissue and brain specimens obtained from his operations and autopsies. This priceless collection, known as the Cushing Brain Tumor Registry (BTR), is preserved at Yale University. Thus, a systematic, in-depth analysis of his work can be performed. In this study, we present a comprehensive analysis of Harvey Cushing's entire CP series,

as documented in the records of the BTR. For a proper assessment of this material, we divided our study into two complementary parts: Part 1 analyzes how Cushing's conception of CPs evolved and the way his clinical and pathological methodology led him to achieve accurate diagnoses, and Part 2 addresses in detail Cushing's surgical strategies and the factors influencing patient outcome.

Methods

Database Generation and Case Selection Criteria

We systematically examined a microfilmed copy of the Cushing BTR stored in the Manuscripts and Archives department at Sterling Memorial Library, Yale University, New Haven, Connecticut (Harvey Cushing Papers, boxes 89–107, <http://hdl.handle.net/10079/fa/mssa.ms.0160>). We retrieved all the clinical charts of the tumors whose diagnosis was compatible with CP, plus two additional cases not identified within the BTR but reported in one of Cushing's papers and in a book reviewing Cushing's work.^{8,10}

Craniopharyngioma Subcohorts Considered

Cushing's series comprises 124 patients with a diagnosis compatible with CP (CP₁₂₄; Table 1). Two subcohorts within this collection are differentiated: 1) a subcohort of pathologically verified CPs (CP₉₂; n = 92), which comprises the patients whose diagnosis was confirmed by Cushing through postmortem examination, histological examination, and/or gross surgical features; and 2) a subcohort of nonverified CPs (n = 32), which comprises the patients

TABLE 1. Harvey Cushing's surgically treated CP series: summary of epidemiological, clinical, pathological, and diagnostic data

Case No.	Patient Initials, Yr of Presentation (surgical ID)	Age (yrs), Sex	Time Course up to Dx	Clinical Symptoms	Major Syndrome	Rx Signs	Diagnostic Evidence/Hist	Topography	Pathology Verified
1	M.D., 1901 (13054)	16, F	3 yrs	H, V, Fr, Som, B, T, C	ITS	Not done	Necr/teratoma	IT	No
2	A.B.W., 1908 (22665)	56, F	14 yrs	H, V, E, Fr, DI, Som, T, A	ITS	SS calcif	Rx/NA	IT	No
3	Unknown, 1909 (NA)	36, F	7 mos	H, V, E, Fr, DI	ITS	S normal	Clin/NA	IT	No
4	L.T., 1910 (25715)	15, F	10 yrs	H, V, E, Fr, DI, T, Szs	ITS	S enlarged	Clin, Rx/NA	S/SS-3V	No
5	E.D., 1910 (26920)	18, F	10 yrs	H, E, Cx, DI, Som, B, T, C	Hyp	S eroded	Clin, Rx/NA	IT	No
6	D.M.B., 1911 (28747)	31, M	4 yrs	H, V, E, Som, B, Me	Hyp	S normal	Necr/papillary	Strict 3V	Yes
7	W.B.T., 1911 (28818)	48, M	5 yrs	H, V, E, DI, Som, B, Me, C	Hyp	S normal	Necr/papillary	IT	Yes
8	I.B.A., 1911 (29150)	33, M	3 yrs	H, V	Chi	S eroded	Necr/adam	S/SS-3V	Yes
9	J.C.A., 1913 (18911)	20, M	7 yrs	H, V, E	Chi-Pi	S calcif	Hist/adam	S/SS	Yes
10	A.L.R., 1913 (41)	25, F	2 yrs	H, V, E, B, Me, Szs	Hyp	SS calcif	Rx, AirV/NA	S/SS-3V	No
11	K.L., 1913 (663)	11, F	6 yrs	H, V, E, B	Chi	SS calcif	Hist/teratoid	Pseudo 3V	Yes
12	O.A.F., 1913 (13-178)	20, M	18 yrs	H, V, E, Som, Szs	HICP	S eroded	Necr/adam	Pseudo 3V	Yes
13	M.N.M., 1913 (75)	58, F	1 yr	V, O, DI	Chi	S enlarged	Clin/NA	NA	No
14	J.C.N., 1913 (22-A)	51, F	1 yr	H, V, Fr, DI	Chi-ITS	S eroded	Clin, Rx/NA	NA	No
15	H.W.F., 1913 (164)	12, M	1 yr	H, V, E, O	Chi-Pi	S eroded	Clin, Rx/NA	NA	No
16	A.F.B., 1913 (209)	28, F	15 yrs	V, E, Fr, DI, Som	Chi-Pi	SS calcif	Clin, Rx /NA	S/SS-3V	No
17	D.A., 1913 (235)	14, F	7 yrs	H, V, Fr, Cx, DI, Som, B, C	All5	SS calcif	Hist/teratoid	S/SS-3V	Yes
18	L.E.M., 1913 (303)	12, M	2 yrs	H, DI, Som, B, Me, T, A, G	Hyp	S normal	Clin/NA	S/SS-3V	No
19	E.S., 1913 (1009)	19, F	13 yrs	H, V, Fr	HICP	S normal	Clin/NA	IT	No
20	B.A., 1913 (538)	51, F	3 yrs	H, V, B, Me, Szs, CN VI palsy	HICP	S eroded	Hist/teratoid	S/SS-3V	Yes
21	A.D.S., 1914 (1036)	41, F	6 mos	H, V, Fr, Som, B, Me	Hyp	S eroded	Necr/teratoid	IT	Yes
22	S.D., 1914 (1033)	30, F	15 yrs	H, V, E, B	Chi-Pi	S/SS calcif	Hist/epith cyst	S/SS	Yes
23	H.B., 1914 (1291)	19, F	7 yrs	H, E, Fr, Som, B, Me	ITS-Hyp	S eroded	Clin, Rx/NA	NA	No
24	E.M.S., 1914 (1440)	49, F	10 yrs	H, V, Fr, Som, B, Me, G	All5	SS calcif	Clin, Rx/NA	NA	No
25	O.M.C., 1914 (1583)	23, F	2 yrs	H, V, E, CN VII palsy	HICP	S normal	Clin/pit cyst	NA	No
26	L.J.B., 1914 (1629)	27, F	1 yr	H, V, E, Szs	Chi-Pi	S enlarged	Surg/pit cyst	Pseudo 3V	Yes
27	B.S.L., 1914 (2114)	40, F	20 yrs	H, V, Fr, DI, Som, B, Me, G	ITS-Hyp	S calcif	Surg/S teeth	S/SS-3V	No
28	D.C., 1914 (2186)	48, M	2.5 yrs	H, V, E, DI	Chi-Pi	S enlarged	Hist/pit cyst	S/SS	No
29	A.L.B., 1914 (2153)	11, F	1 yr	H, V, E, DI	HICP	SS calcif	Necr/SS cyst	IT	Yes
30	C.K., 1914 (2268)	21, M	3 yrs	H, V, B, Me, G, UI, C, Szs	Hyp	S enlarged	Clin, Rx/NA	S/SS-3V	No
31	H.J.B., 1915 (2323)	15, M	3 yrs	V, E, Fr, DI, Som, B, Szs	ITS	S enlarged	Clin, Rx/NA	IT	No
32	T.L.D., 1915 (3185)	20, M	6 mos	H, V, E, Som	Chi-Pi	S enlarged	Hist/cholest	S/SS-3V	Yes
33	H.B., 1915 (3572)	30, M	NA	H, V, E, Som	Chi-Pi	S enlarged	Hist/adam	S/SS	Yes
34	Unknown, 1915 (3883)	30, F	NA	H, V, Fr, Som, Szs	HICP	S enlarged	Surg/pit cyst	S/SS-3V	No
35	M.C.L., 1916 (4306)	23, F	1.5 yrs	H, V, E, Szs	HICP	S eroded	Clin, Rx/NA	S/SS-3V	No
36	M.F.W., 1916 (4487)	31, F	10 yrs	H, V, E, Fr	Chi-Pi	S eroded	Surg/SS cyst	S/SS	No
37	E.C., 1916 (5617)	8, F	3 mos	H, V, B, T, UI, C	HICP	S eroded	Clin, Rx/NA	NA	No
38	M.H.D., 1916 (5839)	20, F	5 yrs	H, V, DI, G	HICP	SS calcif	Surg/SS cyst	Pseudo 3V	Yes
39	L.S., 1917 (6615)	16, F	3 yrs	H, V, E, Fr, DI, Som	HICP	SS calcif	Surg/SS cyst	S/SS-3V	Yes
40	R.I.R., 1919 (11152)	13, M	6 yrs	H, V, E	Chi-Pi	S eroded	Surg/cholest	Pseudo 3V	No
41	L.W., 1919 (10067)	15, F	2 yrs	H, V, E, DI, Som, B, Me, T, G	All5	SS calcif	Hist/dermoid	S/SS-3V	Yes
42	J.P., 1919 (10563)	14, M	4 yrs	H, V, E, Som, B, G	HICP	SS calcif	Necr/adam	IT	Yes
43	F.E., 1919 (10779)	58, F	4 yrs	H, V, E, O	HICP	S enlarged	Hist/cholest	S/SS	Yes
44	W.C.C., 1919 (11306)	34, M	17 yrs	H, V, Fr, DI, B	ITS	S/SS calcif	Hist/adam	Pseudo 3V	Yes
45	J.A.P., 1919 (11541)	17, M	15 yrs	H, V, E, DI, Som, CN III palsy	Chi-Pi	S/SS calcif	Hist/adam	S/SS	Yes
46	J.A.L., 1920 (11764)	30, F	15 yrs	H, V, DI, Som, B	HICP	SS calcif	Surg/SS cyst	S/SS-3V	Yes
47	C.L.A., 1920 (12292)	35, F	2 yrs	H, V, E, DI, Som, B, Me	ITS	S normal	Hist/papillary	IT	Yes
48	M.M.R., 1920 (12502)	18, F	2 yrs	V, E	Chi-Pi	S enlarged	Surg/SS cyst	S/SS	Yes

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Case No.	Patient Initials, Yr of Presentation (surgical ID)	Age (yrs), Sex	Time Course up to Dx	Clinical Symptoms	Major Syndrome	Rx Signs	Diagnostic Evidence/Hist	Topography	Pathology Verified
49	J.J.C., 1920 (13110)	12, M	1 yr	H, V, Dip	Chi	S enlarged	Surg/SS cyst	S/SS-3V	No
50	S.S.N., 1920 (13453)	33, M	2 yrs	H, V, E	Chi-Pi	S eroded	Hist/papillary	Pseudo 3V	Yes
51	B.B., 1920 (13553)	25, F	2 yrs	H, V, Fr	HICP	S eroded	Hist/papillary	Pseudo 3V	No
52	F.S.D., 1921 (35075)	34, M	1.5 yrs	H, V, E, Fr, Som, B	HICP	SS calcif	Necr/adam	S/SS-3V	Yes
53	H.M.S., 1921 (14011)	11, M	5 yrs	H, V, E, O	Chi	S enlarged	Necr/adam	Pseudo 3V	Yes
54	T.D.L., 1921 (14327)	45, F	30 yrs	H, V, Fr, DI, Som, B, Me, T, A	All5	SS calcif	Necr/adam	S/SS-3V	Yes
55	E.P.W., 1921 (14817)	31, F	5 yrs	V, Fr, Som	Chi-ITS	S normal	Necr/adam	IT	Yes
56	M.H.T., 1921 (14996)	57, F	6 yrs	V, DI, O	Chi-ITS	S normal	Hist/papillary	IT	Yes
57	D.E.H., 1921 (17015)	6, F	3 yrs	H, V, O, Szs	HICP	SS calcif	Necr/adam	IT	Yes
58	J.L.K., 1922 (16147)	15, M	2 yrs	H, V, Fr, Som, Me, A, Szs	Chi-ITS	SS calcif	Hist/adam	S/SS-3V	Yes
59	G.H.A., 1922 (16889)	21, M	7 yrs	H, V, Fr, Som, B, Szs	ITS	SS calcif	Necr/adam	S/SS-3V	Yes
60	C.B.H., 1922 (17148)	23, M	15 yrs	H, V, E	Chi-Pi	SS calcif	Hist/adam	S/SS-3V	Yes
61	C.B.M., 1922 (17444)	21, M	7 yrs	H, V, E, Som, Me, Szs, CN III palsy	HICP	S eroded	Clin, Rx/NA	S/SS-3V	No
62	M.E.K., 1922 (17650)	10, F	6 yrs	H, V, E, Cx	Chi-Pi	SS calcif	Hist/adam	Pseudo 3V	Yes
63	B.A., 1922 (17754)	40, M	5 yrs	H, V, E, B, It paresis	Chi	S normal	Hist/cholest	Pseudo 3V	No
64	J.A.D., 1922 (17844)	12, M	6 yrs	V, E, leg paresis	Pi-Chi	SS calcif	Hist/adam	S/SS	Yes
65	A.V.F., 1922 (17876)	13, F	7 yrs	H, V, E, B	HICP	SS calcif	Hist/adam	S/SS-3V	Yes
66	P.S., 1922 (19274)	15, M	2 yrs	H, V, Fr, Som, Szs	Chi-ITS	SS calcif	Necr/adam	S/SS-3V	Yes
67	W.C.C., 1923 (18658)	25, M	10 yrs	H, V, E, Cx	Pi-Chi	SS calcif	Hist/adam	S/SS	Yes
68	H.V.M., 1923 (18686)	6, M	2.5 yrs	H, V, Szs	Chi	SS calcif	Hist/adam	S/SS-3V	Yes
69	J.R., 1923 (18815)	19, F	5 yrs	H, V, E, DI	HICP	SS calcif	Hist/adam	Pseudo 3V	Yes
70	F.W.V., 1923 (18827)	43, M	1.5 yrs	V, H, E, Som, B, Me, G, UI	Hyp	S normal	Hist/papillary	Strict 3V	Yes
71	L.M.K., 1923 (20045)	57, F	6 mos	H, V, O	Chi	S enlarged	Surg/adam	S/SS	Yes
72	M.P., 1923 (20411)	18, F	2 mos	H, V, E, G	HICP	SS calcif	Hist/adam	Pseudo 3V	Yes
73	K.K.S., 1924 (22493)	19, M	10 yrs	H, E, Fr, DI	Pi-ITS	SS calcif	Hist/adam	S/SS	Yes
74	T.H.C., 1924 (20737)	5, M	4 yrs	H, V, Cx, Som, C	Chi	S calcif	Necr/adam	S/SS-3V	Yes
75	A.M., 1924 (20814)	20, F	4 yrs	H, V, Fr, Som, B, Me, C	ITS-Hyp	SS calcif	Hist/mixed	IT	Yes
76	A.G.S., 1924 (22004)	38, M	20 yrs	V, Fr, DI, B, Me, T, G, C	ITS-Hyp	SS calcif	Necr/adam	IT	Yes
77	J.C., 1925 (22999)	10, M	5 yrs	H, V, E	HICP	SS calcif	Hist/adam	S/SS	Yes
78	L.G.B., 1925 (24292)	51, M	3 yrs	H, V, E, Som, B, Me	Hyp	SS calcif	Necr/adam	Strict 3V	Yes
79	M.T.S., 1925 (31011)	62, F	1 yr	H, V	Chi	S normal	Hist/adam	S/SS-3V	Yes
80	L.T., 1925 (28813)	3, F	6 mos	H, V, E, Cx, DI, Som, B	All5	SS calcif	Necr/adam	Pseudo 3V	Yes
81	H.F.M., 1925 (25383)	26, M	2.5 yrs	H, V, E	Chi	S eroded	Necr/adam	S/SS-3V	Yes
82	M.J.R., 1926 (28247)	6, F	1 yr	H, V, E, Fr, DI, Som, CN VI palsy	HICP	SS calcif	Hist/adam	IT	Yes
83	H.L.R., 1926 (25714)	12, M	6 yrs	H, V, Fr, DI, C	HICP	SS calcif	Hist/adam	S/SS-3V	Yes
84	H.W., 1926 (25886)	17, M	4 yrs	V, E, Fr, DI, Som	Chi-Pi	S/SS calcif	Hist/adam	S/SS-3V	Yes
85	E.H., 1926 (27320)	8, M	6 mos	H, V, E, Som, B, Me, G, C	HICP	SS calcif	Rx/NA	S/SS-3V	No
86	A.C.K., 1926 (26734)	25, M	15 yrs	H, V, E, Fr	ITS-Chi	SS calcif	Hist/adam	Pseudo 3V	Yes
87	J.J.S., 1926 (26200)	10, M	5.5 yrs	H, V, E, DI	Chi-Pi	SS calcif	Hist/CP	S/SS-3V	Yes
88	A.F.M., 1926 (26287)	23, M	14 yrs	H, V, E, DI, B, progeria	Chi-Pi	SS calcif	Hist/adam	S/SS-3V	Yes
89	H.M.S., 1926 (26470)	62, F	9 mos	H, V	Chi	S normal	Hist/papillary	Pseudo 3V	Yes
90	L.V., 1926 (26753)	36, M	15 yrs	H, V, E, DI	Pi-Chi	SS calcif	Hist/adam	Pseudo 3V	Yes
91	F.W., 1926 (27041)	27, M	7 yrs	H, V, Fr, DI, B, Me, G, C	All5	SS calcif	Hist/adam	IT	Yes
92	J.A.B., 1926 (27398)	30, F	15 yrs	H, E, DI, Som, B, Me, G, C	All5	SS calcif	Necr/adam	S/SS-3V	Yes
93	A.Z., 1927 (33831)	32, M	6 mos	H, DI, Som, B, Me, G, C, Szs	Hyp	SS calcif	Hist/adam	IT	Yes

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94	M.E.D., 1927 (28383)	8, F	2 yrs	H, V, E, B, Me	HICP	SS calcif	Necr/adam	IT	Yes
95	H.L., 1927 (30302)	13, M	2 mos	H, V, E, DI, Som, B, Me	All5	SS calcif	Hist/adam	S/SS-3V	Yes
96	E.J., 1927 (29467)	6, M	4 yrs	H, V, E, It paresis	HICP	SS calcif	Hist/adam	All intracranial spaces (giant)	Yes
97	R.L.J., 1927 (31011)	6, F	2 yrs	H, V, E, DI, Som, B, G, Szs	All5	SS calcif	Hist/adam	S/SS-3V	Yes
98	J.L.B., 1927 (32940)	6, M	1 yr	H, V, DI, Som, B, Szs	HICP	SS calcif	Hist/RC-CP	IT	Yes
99	H.O.C., 1927 (32718)	24, F	5 yrs	H, V, Som, B, Szs	HICP	3V calcif	Rx/NA	Strict 3V	No
100	E.I.G., 1928 (31094)	20, F	8 yrs	H, V, E, DI, B	Pi-Chi	S eroded	Surg/CP	S/SS	Yes
101	N.C.S., 1928 (31467)	10, F	1.5 yrs	V, Fr, Som, Szs	HICP	SS calcif	Hist/adam	S/SS-3V	Yes
102	N.F.S., 1928 (31979)	50, F	5 yrs	H, V, Fr, Som, UI	Chi-ITS	SS calcif	Hist/adam	S/SS-3V	Yes
103	M.V.O., 1928 (32294)	10, F	7 yrs	H, V, E, O, Som, T, G	HICP	SS calcif	Rx/NA	S/SS-3V	No
104	A.B., 1928 (32298)	22, F	10 yrs	H, V, Fr, DI, Som, B, UI	Chi-ITS	S eroded	Hist/teratoid	S/SS-3V	Yes
105	K.K.S., 1928 (32358)	46, M	6 mos	V, Fr, DI, Som, B, Me, UI	ITS-Hyp	S normal	Necr/adam	IT	Yes
106	L.R.C., 1928 (32590)	40, F	1 yr	H, V	Chi	SS calcif	Hist/adam	Pseudo 3V	Yes
107	S.B., 1928 (32718)	30, M	1 yr	H, V, E, DI	Pi-Chi	S eroded	Surg/CP	S/SS	Yes
108	M.A.L., 1928 (32851)	9, M	3 yrs	H, V, Fr	Chi	SS calcif	Hist/adam	Pseudo 3V	Yes
109	M.V.M., 1929 (33044)	19, F	1 mo	H, V, Fr	HICP	SS calcif	Hist/adam	IT	Yes
110	B.L.E., 1929 (34286)	15, F	2 yrs	H, V, E, DI	Chi-Pi	S calcif	Hist/adam	S/SS	Yes
111	M.H., 1929 (35047)	43, F	2 mos	H, V, E, O, Som, B, T, UI, C	HICP	SS calcif	Necr/adam	IT	Yes
112	N.A.K., 1930 (35581)	16, M	6 mos	V, E	Chi	S enlarged	Hist/adam	S/SS	Yes
113	E.M.L., 1930 (35994)	27, F	10 mos	H, V, E, B, Som, Me, Szs	Hyp	SS calcif	Necr/adam	IT	Yes
114	E.J., 1930 (36672)	22, F	3 yrs	H, V, Fr, DI, Som, T, G, C	ITS-Hyp	S eroded	Necr/xantho	IT	No
115	M.E.P., 1930 (35969)	29, M	3 yrs	H, V, Fr, DI, Som, B, Me, G	ITS-Hyp	S normal	Hist/adam	IT	Yes
116	N.E.C., 1931 (38528)	23, F	10 yrs	H, V, Fr, B, Som, Me, C, Szs	HICP	SS calcif	Necr/adam	IT	Yes
117	S.G.W., 1931 (38556)	6, M	3 yrs	H, V, A, C	HICP	SS calcif	Necr/adam	S/SS-3V	Yes
118	C.E.O., 1931 (39201)	70, F	3 yrs	H, V	Chi	S normal	Hist/CP-RC	S/SS	Yes
119	M.B., 1931 (39270)	21, F	1 yr	H, V, Som, G, CN VII palsy	HICP	S normal	Hist/CP atyp	Strict 3V	Yes
120	A.C., 1932 (40686)	51, F	2 yrs	H, V	Chi	S normal	Hist/adam	Pseudo 3V	Yes
121	M.E.T., 1932 (40786)	40, F	2 yrs	H, V, E, O	Chi	S normal	Hist/papillary	Pseudo 3V	Yes
122	M.S.B., 1932 (40859)	38, M	4 yrs	H, B, O, Me, Som, G, Dip	Hyp	S normal	Hist/papillary	Strict 3V	Yes
123	M.J.C., 1932 (41028)	17, F	5 yrs	H, V, E, G, CN VII palsy, deafness	HICP	SS calcif	Hist/CP odo	Pseudo 3V	Yes
124	I.M.M., 1932 (41416)	56, F	2.5 yrs	H, V, Dip	Chi	SS calcif	Hist/teratoid	Pseudo 3V	Yes

A = autonomous nervous system alterations; adam = adamantinomatous; AirV = air ventriculography; All5 = all 5 syndromes; atyp = atypical; B = behavioral disturbances; C = consciousness impairment; calcif = calcifications; Chi = chiasmatic syndrome; cholest = cholesteatoma; Clin = clinical; CN = cranial nerve; CP = craniopharyngioma; Cx = cachexia; DI = diabetes insipidus; Dip = diplopia; Dx = diagnosis; E = endocrine deficit; epith = epithelial; Fr = Fröhlich syndrome; G = gait disturbance; H = headache; HICP = high intracranial pressure syndrome; Hist = histology; Hyp = hypothalamic syndrome; ID = identification; IT = infundibulo-tuberal; ITS = IT syndrome; Me = memory defect; NA = not available; Necr = necropsy; O = obesity; odo = odontogenic; Pi = pituitary syndrome; pit = pituitary; Pseudo 3V = suprasellar pseudointraventricular; RC = Rathke's cyst; Rx = skull radiograph; S = sellar; Som = somnolence; SS = suprasellar; S/SS = sellar-suprasellar; S/SS-3V = S/SS-secondary intraventricular; Strict 3V = strictly intraventricular; Surg = surgery; Szs = seizures; T = body temperature alteration; teratoid = CP with teratoid features; UI = urinary incontinence; V = visual deficit; xantho = xanthogranuloma; 3V = third ventricle.

with suprasellar tumors without proven CP histology but whose clinicoradiological, surgical, and/or pathological features made it possible to conclude with near certainty the CP diagnosis. Classification of the cases in each subcohort is indicated in the far-right column in Table 1. The inclusion of this nonverified subcohort is required to provide a complete and coherent analysis of Cushing's series

because a significant number of patients were treated with palliative surgical methods during the initial period of his career (1902–1917), making it impossible to pathologically confirm the diagnosis. Nevertheless, these cases were instrumental to Cushing in formulating the diagnostic criteria and surgical strategies that would be employed in subsequent periods. Therefore, with the aim of ensuring

the reliability of our study, only the subcohort of verified CPs (CP₉₂) is used for all analyses involving pathological variables, such as tumor topography.

Variables Analyzed

Table 2 shows the descriptive statistics for the epidemiological, clinical, diagnostic, and pathological variables analyzed in CP₉₂ and the way in which these variables were categorized. The clinical symptoms in each patient were grouped into the following major syndromes:⁷ 1) high intracranial pressure, headache accompanied by vomiting, papilledema, and/or hydrocephalus; 2) chiasmal syndrome, loss of visual acuity or any visual field defect; 3) pituitary syndrome, symptoms of hypopituitarism, including isolated sexual disturbances, hair loss, atrophic skin alterations, and asthenia of unknown origin; 4) infundibulo-tuberal (IT) syndrome, Fröhlich's syndrome (sexual infantilism and obesity), changes in eating behavior, diabetes insipidus (DI), or sleep disturbances, in particular abnormal diurnal somnolence; and 5) hypothalamic syndrome, psychiatric, behavioral, or emotional alterations, including Korsakoff-like memory impairment, abnormal changes in body temperature, gait disturbances, extrapyramidal symptoms, or sphincter incontinence.

Topographical Tumor Classification

Cushing's thorough descriptions of the anatomical CP-brain relationships, assessed both during the surgical procedure and in postmortem studies, provided precise written and/or pictorial information about the topography of these tumors in most patients (Fig. 2). We classified CP topography according to two major criteria: 1) anatomical compartments occupied by the lesion (sellar, suprasellar, and/or third ventricle [3V]); and 2) type of anatomical deformation of the 3V floor (3VF; integrity, displacement, or encroachment). Our interpretation of the anatomical CP-brain relationships provided by Cushing's surgical annotations and/or illustrative sketches was made in a consensual way by the two main authors (J.M.P. and R.P.). After incorporating this information into our topographical scheme, which has proven highly useful for predicting the severity of hypothalamic damage caused by tumor,^{28,29,32,33} we classified the CP topography in Cushing's series into five categories: 1) sellar/suprasellar CPs, which exclusively occupy the sellar and/or suprasellar compartments; 2) suprasellar-pseudointraventricular CPs, which occupy the suprasellar cistern and cause upward displacement of the 3VF; 3) secondary intraventricular CPs, which extend from the sellar and/or suprasellar compartments into the 3V after breaking through the 3VF; 4) IT or not strictly intraventricular CPs, tumors that develop in the 3VF and replace the infundibulum and tuber cinereum as they grow; and 5) strictly intraventricular CPs, which grow within the 3V, above an intact 3VF. To ensure the accuracy and reliability of this scheme, the topographic analyses were only performed for CP₉₂.

Statistical Analysis

Statistical analyses were performed using SPSS software (IBM SPSS Statistics for Windows, version 24.0, IBM Corp.). Frequencies and descriptive statistics on the

TABLE 2. Categorization of epidemiological, clinical, and pathological variables analyzed in Cushing's CP₉₂ series

Variable	No. of Cases (%)	No. of Cases w/ Valid Data
M/F sex	45 (48.9%)/47 (51.1%)	92
Age		92
≤19 yrs	38 (41.3%)	
20–49 yrs	43 (46.7%)	
≥50 yrs	11 (12%)	
Time course up to diagnosis		90
≤6 mos	11 (12.2%)	
6 mos–1 yr	10 (11.1%)	
1–3 yrs	26 (28.9%)	
3–5 yrs	16 (17.8%)	
>5 yrs	27 (30%)	
Prevalence of major clinical syndromes		92
HICP	61 (66.3%)	
Pituitary	62 (67.4%)	
Chiasmal	74 (80.4%)	
IT	38 (41.3%)	
Hypothalamic	24 (26.1%)	
Clinical variable		
Headache	86 (93.5%)	92
Visual deficits	89 (96.7%)	92
Endocrine deficits	70 (76.1%)	92
Fröhlich syndrome	32 (34.8%)	92
Obesity	37 (40.2%)	92
Cachexia	8 (8.7%)	92
DI	34 (37.0%)	92
Hypothalamic disturbances	35 (38.0%)	92
Somnolence	43 (46.7%)	92
Memory defect	22 (24.4%)	90
Psychiatric disturbances	43 (46.7%)	92
Gait disturbance	16 (17.4%)	92
Neurological deficits	20 (21.7%)	92
Consciousness impairment &/or seizures	19 (20.7%)	92
Diagnostic variables		
Diagnostic methodology		92
Clin & ophthalmic	5 (5.4%)	
Clin, ophthalmic, & Rx	73 (79.3%)	
Clin & AirV	14 (15.2%)	
Rx sign		92
Normal sella	12 (13.0%)	
Eroded sella outline	7 (7.6%)	
Enlarged & eroded sella	12 (13.0%)	
Hyperostosis	2 (2.2%)	
S/SS calcifications	59 (64.1%)	
Pathological variables		
Tumor topography		92
S/SS	16 (17.4%)	
Pseudo 3V	20 (21.7%)	
S/SS-3V	30 (32.6%)	
IT	21 (22.8%)	
Strict 3V	5 (5.4%)	

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TABLE 2. Categorization of epidemiological, clinical, and pathological variables analyzed in Cushing's CP₉₂ series

Variable	No. of Cases (%)	No. of Cases w/ Valid Data
Pathological variables (<i>continued</i>)		
Hydrocephalus	58 (63.0%)	92
Tumor size		92
<2 cm	1 (1.1%)	
2–3.9 cm	47 (51.1%)	
4–6 cm	31 (33.7%)	
>6 cm	13 (14.1%)	
Tumor shape		89
Rounded	21 (23.6%)	
Elliptical	20 (22.5%)	
Multilobulated	36 (40.4%)	
Pear-like	12 (13.0%)	
Tumor consistency		92
Pure solid	5 (5.4%)	
Pure cystic	36 (39.1%)	
Mixed solid-cystic	37 (40.2%)	
Cystic-basal solid	14 (15.2%)	
Histological type		92
Not specified	11 (12.0%)	
Adamantinomatous	67 (72.8%)	
Squamous-papillary	10 (10.9%)	
Mixed	4 (4.3%)	
Degree of adherence*		82
Loose/dissectable	8 (9.8%)	
Tight to sella/gland	16 (19.5%)	
Tight to stalk/chiasm	7 (8.5%)	
Tight to outer 3VF	17 (20.7%)	
Ring-like to 3VF/3V	18 (22.0%)	
Replacement of 3VF	7 (8.5%)	
Tight to all structures	9 (11.0%)	
Calcifications	65 (71.4%)	91
Peritumoral gliosis	54 (71.1%)	76

* An accurate definition of CP adherence categories is provided in Prieto et al., 2016.

variables under study were obtained. Bilateral correlations between pairs of categorical variables were tested using the asymptotic chi-square test or the Monte Carlo exact test. Significance was assumed at a probability value less than 0.05.

Results

Cushing's CP Series: Demographic and Clinicopathological Features

Table 1 presents a summary of the epidemiological, clinical, and pathological features of the 124 patients that form CP₁₂₄. A rather balanced distribution between the sexes was observed (male/female ratio: 0.95), with CP incidence peaks in young patients 10–19 years old (29%) and the other in middle-aged patients 30–49 years old

(25%; Fig. 3A). The distribution of CP patients that Cushing treated in every 5-year period throughout his career is shown in Fig. 3C. The incidence rates for the individual symptoms analyzed in CP₁₂₄ are shown in Fig. 4A.

Within CP₉₂, the three most common clinical syndromes observed at the time of diagnosis, isolated or in combination, were loss of vision caused by chiasm compression (80%), hormonal deficits from pituitary insufficiency (67%), and headache and/or vomiting due to high intracranial pressure (66%; Table 2). Patients exhibited drowsiness in 47% of the cases, whereas a frankly comatose status occurred in 12%. Clinical and/or radiological signs of obstructive hydrocephalus were identified in 63% of patients. Preoperative signs of DI were reported in 37%. Interestingly, nearly half of the patients (47%) manifested life-hampering neuropsychological or psychiatric disturbances, among them a severe cognitive deterioration associated with impaired short-term memory and confabulation similar to Korsakoff psychosis in 24%.

The presumed preoperative diagnosis of CP was supported by findings of the funduscopic exam and skull radiography in 95% of patients. Within the CP₉₂, abnormal funduscopy results were described in 93.5%, with signs of retinal atrophy in 58%, papilledema in 16%, and papilledema superimposed on atrophy in 16%. Skull radiographs displayed hyperdense shadows compatible with suprasellar calcifications in 64% of patients, an enlarged sella turcica in 13%, and a normal-sized sella, with or without erosion of its outline, in 23%. Additional air ventriculography exams were performed in only 15.2% of patients (Table 2).

Distribution of tumor topographies in the CP₁₂₄ cohort is shown in Fig. 3B, and those corresponding to CP₉₂ are described in Table 2. The majority of tumors (60.8%) in CP₉₂ occupied the 3V cavity at the time of surgery, either because they had developed primarily within the 3VF (28%) or because they had broken through the 3VF from an original extraventricular position (33%). The rest of the lesions had developed originally from the pituitary gland-stalk complex, beneath the 3VF (39%). Almost half of the tumors were large (over 4 cm), and the predominant consistency was mixed solid-cystic (40%). A multilobulated-shaped tumor was the most common morphology observed (40.4%). The adamantinomatous histological variant was confirmed in 73% of the CP₉₂ subcohort.

Strong tumor adhesions to the 3VF or 3V walls were observed during the surgical procedure in 62% of cases (Table 2). In the majority of strongly attached CPs, the tumor presented the most severe morphological pattern of adherence to the hypothalamus (ring-like attachment to the 3VF or replacement of the 3VF in 66.6%), the ones associated with the highest surgical risk.³⁸ This is consistent with the 71% rate of peritumoral gliosis observed in the histological studies.

Relationships Between Epidemiological and Clinicopathological Variables

Table 3 shows the most relevant relationships found between pairs of epidemiological, clinical, and/or topographical/pathological CP features within Cushing's series. The highest rate of endocrine deficits was observed in the pediatric population ($p < 0.001$), whereas IT and hypo-

FIG. 2. Midsagittal tumor sections from autopsy specimens showing the five major tumor topographies evidenced in Cushing's CP₉₂ series. **A:** Sellar/suprasellar: tumor occupies both the sellar and suprasellar compartments beneath an intact 3VF. **B:** Pseudo-intraventricular: this suprasellar tumor causes upward displacement of the 3VF, mimicking an intraventricular position. **C:** Sellar/suprasellar-secondary intraventricular: a sellar and/or suprasellar lesion that eventually invades the 3V after breaking through the 3VF (case 75). **D:** Infundibulo-tuberal: tumor develops within the nervous tissue of the 3VF (within the infundibulum and/or tuber cinereum) and predominantly expands within the 3V (case 21). **E:** Strictly intraventricular: tumor primarily originates within the 3V, above an intact 3VF (case 6). Panels A, B, and E from Cushing: *The Pituitary Body and Its Disorders*, JB Lippincott, 1912. Public domain. Panel D from Walker: *Arch Ophthalmol* 45:407-437, 1916. Public domain. Panel C reproduced from Cushing's BTR. Public domain. Courtesy of the Manuscripts and Archives department of the Sterling Memorial Library, Yale University. **F:** Bar chart showing the relationship between the tumor topography and the histological variant in CP₉₂. Note the lack of papillary cases among the sellar/suprasellar and secondary intraventricular topographies and the predominance of this histological variant in the group of strictly intraventricular CPs ($p < 0.001$). S = sellar; SS = suprasellar. Figure is available in color online only.

thalamic syndromes were mainly reported among adults older than 30 years of age ($p = 0.01$). Hydrocephalus occurred predominantly among children and young patients, a finding related to the development of giant ($p = 0.05$) and multilobulated ($p = 0.04$) tumors in these age groups (Fig. 4B). The squamous-papillary type was diagnosed almost exclusively among adults over 40 years old ($p < 0.001$; Fig. 4C). In contrast, the highest rate of calcifications, typical of the adamantinomatous variant, occurred among patients under 20 years old ($p < 0.001$).

Clinical and Pathological Features Depending on CP Topography

Craniopharyngioma topography was the variable showing the most robust relationships with the presence of certain groups of symptoms in the CP₉₂ subcohort (Table 3). The highest rate of symptoms due to hypothalamic dysfunction, including Fröhlich syndrome, DI, abnormal

somnolence, memory deficits, and psychiatric disturbances, was observed among CPs developing primarily within the 3VF (IT topography), as well as among those tumors invading the 3V after breaking through the 3VF (sellar/suprasellar-intraventricular topography; $p < 0.001$). Both topographies largely replaced the 3VF and presented the strongest and riskiest adherences to the hypothalamic remnants ($p < 0.001$), a fact linked to the highest rate of irreversible hypothalamic injury after Cushing's attempts to remove these types of lesions ($p < 0.001$). The fundamental influence that CP topography had on patient outcome will be addressed in detail in Part 2 of this study.

Discussion

The "Interpeduncular Tumor": A Lesion Type That Marked Cushing's Career

A quirk of fate inescapably bound Harvey Cushing's

FIG. 3. Epidemiological and topographical characterization of Cushing's CP₁₂₄ series. **A:** Histogram of age distribution. Half of the patients are between the ages of 10 and 29 years old. **B:** Bar graph showing the distribution of CP topographies. Sellar-SS = sellar/suprasellar (15%); SS-Pseudo 3V = suprasellar pseudointraventricular (19%); Secondary 3V = sellar/suprasellar–secondary intraventricular (33%); Infundibulo-Tuberal = not strictly intraventricular (25%); 3V-Strict = strictly intraventricular (5%). **C:** Bar graph displaying the number of patients treated by Cushing for the time periods indicated. Note that the proportion of verified cases was higher from the 1920s onwards, coinciding with the refinement of diagnostic and histological methods. The low number of cases treated between 1916 and 1920 is due to Cushing's service during World War I.

career to CPs. Shortly upon his return from his year's sojourn in Europe, in December 1901, Cushing was confronted with his first "neurosurgical case" at Johns Hopkins, a kind of enigmatic intracranial lesion in a 16-year-old female named Mary D.^{14,16} This patient suffered from the same symptoms of sexual infantilism and obesity described by Alfred Fröhlich only a few months earlier, in a case that gave rise to the definition of Fröhlich's syndrome.²² Despite Cushing's efforts to alleviate his patient's severe intracranial pressure by performing three consecutive decompressive craniectomies, she eventually died, and a large, calcified cyst embedded in the infundibulum was found during her necropsy. Cushing drew an intricate sketch of the tumor, considered a teratoma at that time (Fig. 1B). Some years later, he acknowledged that the true pathological nature of this "interpeduncular tumor" was that of a CP.^{12,23,31} Eventually, the tumor specimen was lost, resulting in Cushing's determination to maintain all files and pathological specimens from his surgical patients, which served as the origin of the BTR, one of Cushing's greatest legacies and the source of information allowing for, a century later, the scientific analysis of his CP series.

Cushing's Insights Toward a Precise Characterization of CPs

At the time that Cushing published his acclaimed monograph on pituitary tumors in 1912, he had already treated eight interpeduncular tumors with discouraging results (cases 1–8; Table 1).^{14,18} Unlike pituitary gland "strumas" (i.e., macroadenomas), these interpeduncular lesions posed a formidable diagnostic and therapeutic

challenge owing to their suprasellar location above a usually normal-sized sella turcica.^{30,34} Toward the end of 1911, Cushing found two epithelial cysts within the 3V in the brain specimens of two adults who had died, each after a short-term illness marked by severe psychiatric disturbances.¹⁴ Puzzled by the location and histology of these tumors, he named them "papillary infundibular cysts" in his pituitary monograph without acknowledging that they actually corresponded to the squamous-papillary variant of hypophyseal duct tumors, the entity categorized by the Austrian pathologist Jakob Erdheim (1874–1937) in 1904.²¹

Before Erdheim's seminal work defining the new category of hypophyseal duct tumors (CPs), a great number of rather confusing terms had been employed to describe the suprasellar tumors with the pathological features typical of CPs.^{6,35} Many of these lesions were included under the common category of "pituitary cysts," whereas most of them actually originated above an intact pituitary gland. Aware of this fact, Cushing favored the anatomical over the histological viewpoint by initially adopting the term "suprasellar cyst" to refer to the type of interpeduncular tumor he had first identified in 1901. Between 1911 and 1921, he used the terms "suprasellar" and "interpeduncular" interchangeably to refer to the group of congenital tumors presumably derived from cell inclusion (anlage) of either Rathke's pouch or its ascending buccal-cranial pathway, the hypophyseal duct in early embryonic life.^{14,18} It appears that Cushing purposely avoided the term "hypophyseal duct tumor" introduced by Erdheim, despite knowing of and mentioning Erdheim's paper in his 1912 magnum opus on the pituitary gland.¹⁴ Curiously, Percival Bailey (1892–1973), a neurosurgical trainee of Cushing,

FIG. 4. Clinical and histological characterization of Cushing's CP series. **A:** Bar graph displaying the distribution of the main clinical symptoms in CP₁₂₄. Dark green area within each bar represents the cases within each category presenting with hydrocephalus or symptoms of intracranial hypertension (ICH). Headache (95%), endocrine deficits (76%), and severe visual deficits (Visual [sev]; 68%) were the most common symptoms in this cohort. **B:** Correlation between age and the presence of hydrocephalus or symptoms of ICH in CP₉₂. Note that 76% of patients under 20 years of age suffered from ICH symptoms ($p < 0.001$). **C:** Relationship between age and histological variant in the CP₉₂. Note that all papillary CPs were diagnosed in patients ≥ 20 years of age ($p < 0.001$). Figure is available in color online only.

continued to employ Erdheim's term in his pathological studies on Cushing's CP cases.^{1,3,37}

Throughout most of the 1920s, Cushing preferentially employed the misnamed terms "pharyngeal pouch cyst" or "craniopharyngeal pouch cyst" despite the well-established concept that the adenohypophyseal primordium, or Rathke's pouch, originates from the embryo's primitive buccal cavity (stomodeal epithelium), not from the pharynx.^{27,39} Cushing himself picked the catchy term "craniopharyngioma" in 1929, adding the Greek suffix "-oma" (meaning "swelling" or "tumor") to the combination of "cranio" and "pharynx," and he employed it for the first time in the patient B.L.E. (case 110; Table 1 and Fig. 1C). He chose this designation to highlight the congenital nature of these extremely heterogeneous, epithelial tumors, presumably derived from the pituitary primordium. This concept was practically the same as the one proposed by Jakob Erdheim.³⁶ Cushing incorporated this new term into his three major monographs addressing this type of tumor; thus, this moniker spread worldwide and ultimately prevailed over Erdheim's terminology.^{9,11,13}

Cushing's Clinical Assessment of CP Patients: An Open Window Into the Workings of the Brain

Craniopharyngioma treatment posed enormous tech-

nical challenges to Harvey Cushing, yet it also provided an endless supply of insight regarding a wide range of endocrinological and neuropsychological disturbances caused by these tumors.^{2,13,24} As a type of lesion primarily involving the infundibulum and adjacent hypothalamus, CPs definitely served to shed light on the separation of hypothalamic and hypophyseal functions.^{7,31,32} Alfred Fröhlich's 1901 identification of the adiposogenital syndrome enabled Cushing to preoperatively diagnose CPs, especially among children and young patients manifesting DI (Fig. 5A1 and A2).²² But rather than suspecting hypothalamic dysfunction, Cushing initially considered Fröhlich's syndrome to involve tumors blocking the passage of pituitary gland secretions into the 3V, secretions he thought were essential for adequate brain control of body homeostasis.³¹ Notably, it was Percival Bailey who proved incontrovertibly that DI and Fröhlich's syndrome were generated by lesions restricted to the hypothalamus.⁴ Bailey also provided the important concept that a specific set of symptoms observed in CP patients, such as hypersomnia and personality and/or behavioral changes, represents true hypothalamic alterations.² In his 1930 lecture to the Royal College of Surgeons in London, Cushing acknowledged Bailey's important contributions and summed up the clinical and anatomical evidence provided by CP patients regarding the newly recognized "hypothalamic

TABLE 3. Bivariate relationships between epidemiological, topographical, and pathological categories analyzed for Cushing's surgically treated CP series, 1901–1932

Variable	p Value	Specific Relationship
Related to age (CP ₁₂₄)		
Hydrocephalus	<0.001	Highest rate of hydrocephalus in patients younger than 30 yrs
Major syndrome	0.01	Highest rate of IT/hypothalamic syndrome in patients older than 30 yrs
Endocrine symptoms	<0.001	Highest rate of endocrine deficits in group 10–19 yrs old
Memory disturbances	0.029	Highest rate among adult patients older than 20 yrs
CP size	0.05	Highest rate of large lesions (4–10 cm) in pediatric group (age <20 yrs)
CP shape	0.04	Highest rate of multilobulated lesions in pediatric group (age <20 yrs)
CP histology	<0.001	Highest rate of squamous-papillary variant in group 40–69 yrs old
CP calcifications	<0.001	Highest rate of calcifications in pediatric group (age <20 yrs)
Related to CP topography (CP ₉₂)		
ITS	<0.001	Highest rate in IT & S/SS-3V CPs
Hypothalamic syndrome	<0.001	Highest rate in S/SS-3V & 3V CPs
Fröhlich syndrome	0.029	Highest rate in IT & S/SS-3V CPs
Psychiatric disturbances	0.03	Highest rate in IT, S/SS-3V, & 3V CPs
Somnolence	<0.001	Highest rate in IT & 3V CPs
Memory disturbances	<0.001	Highest rate in S/SS-3V & IT CPs
Consciousness disturbances	0.002	Present almost exclusively in S/SS-3V & IT CPs
DI	0.06	Highest rate among IT CPs
Hydrocephalus	<0.001	Highest rate of hydrocephalus w/ S/SS-3V CPs
CP shape	<0.001	Highest rate of rounded lesions among IT CPs
CP histology	0.007	Highest rate of squamous-papillary type in IT and 3V CPs
CP adherence	<0.001	Replacement of 3VF only in IT CPs
Related to CP pathological features (CP ₉₂)		
CP size & tumor adherence	0.01	Highest rate of strong adherence to 3V in CPs 4–6 cm
CP consistency & tumor adherence	0.002	Highest rate of strong adherence to all brain structures in mixed solid-cystic tumors; highest rate of 3VF replacement in cystic-basal solid CPs
CP histology & adherence	0.008	Highest rate of strong CP adherences in adamantinomatous type; highest rate of pedicle attachment in squamous-papillary type
CP adherence & postop hypothalamic injury	0.003	No hypothalamic injury when CPs have loose adherence; hypothalamic injury in >85% of CPs w/ 3VF replacement

doctrine” for a central, hypothalamic control of body metabolism and water homeostasis.¹³

Harvey Cushing was also the first author to take interest in the behavioral and psychological disturbances manifested by CP patients.¹⁵ Clinical and pathological evidence provided by Fulton and Bailey in 1929 conclusively proved that these symptoms had a primarily hypothalamic origin.²⁴ The analysis of Cushing's entire CP series shows that the rate of patients manifesting severe pre- or post-operative neuropsychological or psychiatric disturbances that hampered their quality of life to the point of forcing them to quit their jobs or school and/or affected their interpersonal relationships reached 45% (57 patients). Among these disturbances, severe cognitive deterioration including a marked short-term memory deficit similar to Korsakoff psychosis (in 24% of the CP₁₂₄), a status of emotional lability including rage attacks (in 16%), and/or an apathetic attitude or permanent disinterest in their own lives (in 9%) were the predominant alterations. Such disturbances were chiefly observed in patients with CPs developing primar-

ily within the 3VF (in 33% of IT CPs) and in large tumors invading the 3V (in 44% of 3V-invading CPs).

Cushing's Methodology and Rationale for CP Diagnosis

Craniopharyngioma diagnosis during Cushing's time at the Peter Bent Brigham Hospital (1912–1932) involved a great deal of uncertainty. The only available methods for the preoperative diagnosis of pituitary tumors were systematic clinical and neurological explorations such as fundoscopic exams and identification of sella turcica alterations on skull radiographs.^{10,16,30,34} Despite the rudimentary nature of these tools, Harvey Cushing decisively contributed to the refinement of the clinical and radiological clues allowing for differentiation between pituitary adenomas and CPs with reasonable accuracy.

Ophthalmoscopic retinal exams were fundamental for Cushing to successfully develop a neurosurgical program for pituitary tumors. He soon learned how to identify the presence of choked discs (papilledema), the objective sign of high intracranial pressure through which the presence

FIG. 5. Harvey Cushing's methodology for CP diagnosis. Fröhlich's syndrome phenotype: a 12-year-old boy with incipient feminine-type obesity and failed sexual development (J.A.D., case 64, **A1**) and a young woman, 19 years old, with amenorrhea and marked obesity (H.B., case 23, **A2**). Perimetry exam showing bitemporal hemianopia, a visual defect characteristic of the optic chiasm injury caused by CPs (J.C.A., case 9, **B**). Lateral skull radiograph of J.A.B. (case 92, **C**), obtained in October 1926, showing dense suprasellar shadows just above the sella turcica, the radiological correlate of tumor calcifications. Picture of tumor specimen removed from D.A. (case 17, **D**) in June 1913. **FIG. 5. (continued)**→

FIG. 5. Note the multilobulated, solid-cystic structure of the lesion, whose hard capsule was tightly adhered to the vessels of the circle of Willis. This patient died shortly after tumor removal because of the severe intraoperative bleeding and permanent hypothalamic injury caused by en bloc resection of the mass. Sketch of the microscopic appearance of a typical CP, created by Louise Eisenhardt (1891–1967), Cushing's associate neuropathologist, on April 10, 1931 (S.G.W., case 117, E1). Examination of the solid tumor portion via the supravital technique showed epithelial cells arranged in concentric masses or whorls (a) and cholesterol crystals (b). Handwritten description (E2) of histological characteristics of tumor featured in E1, by Louise Eisenhardt. Reproduced from Cushing's BTR. Public domain. Courtesy of the Manuscripts and Archives department of the Sterling Memorial Library, Yale University.

of an intracranial tumor could be presumed.^{34,35} However, the observation of macular atrophy instead of papilledema was a finding typically reported for CP patients.⁴⁰ This localizing sign, indicating direct optic chiasm compression by a suprasellar mass, in combination with symptoms of hypophyseal insufficiency, helped Cushing to differentiate suprasellar lesions from large intracranial tumors involving other locations.

Clifford B. Walker (1884–1943), an ophthalmologist collaborating with Cushing at Peter Bent Brigham, described the specific campimetric defects associated with optic chiasm distortions by pituitary tumors.⁴⁰ Bitemporal hemianopia was identified as a rather specific visual deficit due to injury caused to the central portion of the chiasm by the tumor bulk (Fig. 5B). It was observed in 26 of 81 patients with large hypophyseal and parhypophyseal tumors. Four of these cases corresponded to CPs. After these studies, routine campimetric and funduscopy exams were performed for the majority of Cushing's CP patients, as reported in the BTR. Bitemporal and concentric campimetric deficits associated with optic atrophy in patients manifesting the triad of severe headache, loss of vision, and Fröhlich's syndrome formed the basis for the clinical suspicion of CP.³⁴

In 1914, an important radiological study by Alfred Luger (1886–1938), the first full-time radiologist at the Peter Bent Brigham Hospital, identified the distinctive radiographic sign of nodular hyperdense shadows above or within the sella turcica in three CPs, the correlate of calcareous depositions within the tumor.²⁵ Merrill Clary Sosman (1890–1959), a neuroradiologist who started collaborating with Cushing in 1922, significantly improved the detection of intracranial calcifications with skull radiographs and, in 1924, conclusively proved the value of this sign for accurate preoperative diagnosis of calcified CPs, which represented 71% of the cases in Cushing's series (Fig. 5C).²⁶

Cushing's use of air ventriculography for CP diagnosis would be postponed until the final stage of his career.³⁴ Cushing first tested this method in 1919 (case 45; Table 1), yet his personal animosity toward Walter Dandy (1886–1946), his former trainee at Johns Hopkins and the inventor of air ventriculography in 1918, undoubtedly influenced his dismissal of this valuable technique, which he only used occasionally before 1928.^{20,41} Afterward, Cushing acknowledged its utility in outlining CP boundaries as well as 3V occupation by the tumor. Air ventriculography would prove essential for implementing the new intraventricular approaches employed by Cushing to gain direct access to 3V CPs. In his last monograph on meningiomas, published in 1938, Cushing praised "Dr. Dandy's brilliant and useful discovery" (page 522) and admitted that he had

restricted its use because of an overly conservative attitude and unfounded fear regarding the risks associated with air ventriculography.¹⁹

Hypothalamus Involvement in Cushing's CP Series: The Major Determinant of Surgical Risk

For a long period, Cushing overlooked the anatomical evidence that many CPs occupied a high position within the infundibulum and 3V, as confirmed in many necropsy studies in his own patients (Figs. 1B and 2A–E). Although he initially rejected Erdheim's claims that CPs primarily involved neural centers at the base of the 3V (i.e., the hypothalamus),²¹ roughly 60% of the tumors in CP₉₂ primarily expanded within the hypothalamus (IT and 3V CPs) or had encroached upon this region from the sellar/suprasellar compartments (secondarily intraventricular CPs; Fig. 2C–E). Most of these patients manifested symptoms related to hypothalamic dysfunction. After a systematic examination of Cushing's CP autopsy specimens, Percival Bailey was unable to discriminate tumor boundaries from the adjacent hypothalamus; consequently, he considered these lesions as true "tumors of the hypothalamus."²²

The extensive, strong tumor adherences to the hypothalamus usually present in CPs involving the 3V represent a critical factor, accounting for the high mortality associated with the surgical removal of these tumors in Cushing's series (Fig. 2D and Table 3).³⁸ Early on, Cushing noticed the intractable hyperthermia and permanent lethargic condition that usually followed surgical attempts at CP removal when the tumor strongly adhered to the hypothalamic region. In 90% of the deaths occurring in the first 8 weeks after surgery (25 of 28 patients), mortality was directly related to hypothalamic damage. This injury resulted from the removal of portions of the hypothalamus strongly adhered to the tumor capsule (12 patients) or was attributable to a delayed hypothalamic failure some days or weeks after the procedure, caused by ischemic or hemorrhagic diencephalic injury (Fig. 2D). Postoperative hypothalamic dysfunction could not be offset with corticosteroids or hormone replacement therapy at that time. Accordingly, Cushing's goal was to find new surgical methods to provide optimal visualization and safe dissection of CPs tightly attached to the hypothalamus.^{31,37} These methods will be properly addressed in Part 2 of this work.

Conclusions

Analysis of Cushing's CP series is meaningful for neurosurgeons today as it shows the nature of the main problem posed by these complex lesions: the high risk of hypothalamic injury associated with their removal. The clinical insights, pathophysiological concepts, and diag-

nostic methodology implemented by Harvey Cushing in CP treatment contributed much to establishing the foundation for modern neurosurgical understanding of this tumor type. Cushing's legacy to modern CP neurosurgery can be summed up in four key points: 1) the categorization of clinical symptoms specifically derived from either hypothalamic dysfunction or hypophysial insufficiency; 2) the accurate description of anatomical CP-brain relationships; 3) the development of a rational protocol for CP topography diagnosis based on neuroophthalmological and radiological data; and 4) the exploration of all possible surgical avenues to these deep-seated tumors, including the set of intraventricular techniques necessary for the safe removal of CPs involving the hypothalamus.

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Disclosures

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Author Contributions

Conception and design: Pascual, Prieto. Acquisition of data: Pascual, Prieto. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: Pascual. Reviewed submitted version of manuscript: Pascual, Prieto. Approved the final version of the manuscript on behalf of all authors: Pascual. Statistical analysis: Barrios.

Supplemental Information

Companion Papers

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Correspondence

José María Pascual: La Princesa University Hospital, Madrid, Spain. jmpasncj@hotmail.com.