Antibodies Against Hypothalamus and Pituitary Gland in Childhood-Onset Brain Tumors and Pituitary Dysfunction

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BACKGROUND and AIM

Antipituitary (APA) and antihypothalamus antibodies (AHA) have not been investigated in children and adolescents with brain tumors.

Aim: to detect the presence of APA and AHA in patients treated for brain cancers, and their association with pituitary dysfunction

SUBJECTS and METHODS

Sixty-three patients with craniopharyngioma, glioma and germinoma treated with surgery and/or chemotherapy and/or radiotherapy were evaluated at a median age of 13 years.
Forty-one had MPHD, 6 had a single defects being GH the most common (65.1%), followed by AVP (61.9%), TSH (57.1%), ACTH (49.2%) and gonadotropin (38.1%) **(Table 1).** APA and AHA were evaluated by indirect immunofluorescence in patients and in fifty controls.

RESULTS

APA and/or AHA were detected in half of the patients but not in the controls (P<0.001); 25 were APA (P=0.001), 26 were AHA and 20 were both APA and AHA positive (P<0.001), mostly with germinoma **(Fig 1; Table 2)**.

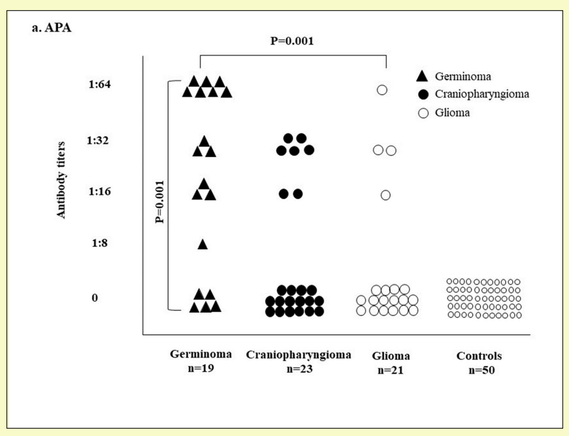
APA (P<0.001) and their titers (P=0.008) were significantly associated with the number of pituitary defects **(Fig 2)**, with a 25% risk of developing an additional pituitary defect at each increase in antibody titers from one level to a higher one; this risk was confirmed also after correction for tumor type (18.4%, p=0.002). A similar relation was found for AHA (P=0.038). There was a significant association between the presence of APA and radiotherapy (P=0.03) **(Fig 3).**

Table 1 Clinical characteristics and treatment of 63 patients with brain tumors according to the type of tumor

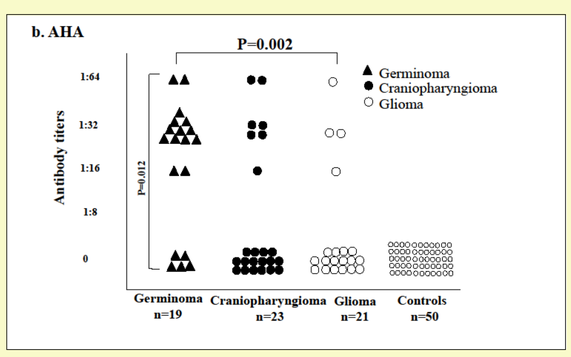
	Craniopharyngiomas n=23 Median, IQR	Gliomas n=21 Median, IQR	Germinomas n=19 Median, IQR
Age at tumor diagnosis (years)	8.7 (4.8 - 10.0) [a,b,c]	3.5 (2.0 - 6.8)	11.5 (10.5 - 14.5)
Time between diagnosis and Antibodies assessment (years)	7.0 (13.2 - 2.7) [d]	5.2 (2.2 - 6.8)	4.1 (1.4 - 1.7)
Pituitary defects at Antibodies assessment	4 (3-5) [e]	0 (0-1) [b]	4 (3-5)
	(n, %)	(n, %)	(n, %)
AVPD	21 (91.3) [e]	1 (4.8) [b]	17 (89.5)
GHD	19 (82.6) [e]	5 (23.8) [b]	17 (89.5)
TSHD	20 (87.0) [e]	2 (9.5) [b]	14 (73.7)
ACTHD	17 (73.9) [e]	1 (4.8) [b]	13 (68.4)
GND	13 (56.5) [e]	1 (4.8) [g]	10 (52.6)
Males (n=34)	12 (52.2)	10 (47.6)	12 (63.2)
Females (n=29)	11 (47.8)	11 (52.4)	7 (36.8)
Surgery (n=32)	22 (95.7) [a,f]	5 (23.8)	5 (26.3)
Radiotherapy (n=46)	16 (69.6)	11 (52.4)	19 (100) [g]

IQR (Interquartile Range)
[a] p < 0.01 Craniopahryngiomas *vs* germinomas; [b] p<0.001 Germinomas vs gliomas; [c] p<0.05 Craniopharyngiomas vs gliomas;
[d] p=0.088 Craniopharyngiomas *vs* germinomas; [e] p<0.001 Craniopharyngiomas vs gliomas; [f] p<0.001 Craniopahryngiomas *vs* germinomas
[g] p<0.01 Germinomas vs gliomas; Abbreviations: AVPD= vasopressin deficiency; GHD= growth hormone deficiency; TSHD= central hypothyroidism; ACTHD= central adrenal insufficiency; GND= hypogonadotropic hypogonadism

Fig. 1 Distribution of APA and AHA in 63 patients with brain tumors according to the diagnostic category

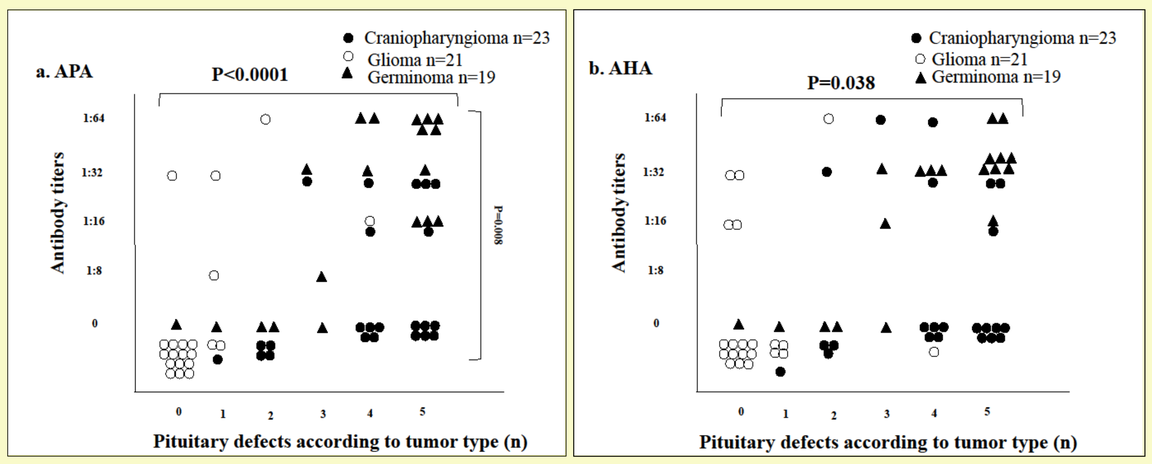


PANEL A
The presence of APA (P=0.001) and their titers (P= 0.001) were significantly associated with the type of tumor in the following order: germinomas, craniopharingyomas and gliomas



PANEL B
The presence of AHA (P=0.002) and their titers (P= 0.012) were significantly associated with the type of tumor in the following order: germinomas, craniopharingyomas and gliomas

Fig 2 Distribution of APA and AHA in 63 patients with brain tumors based on tumor type and pituitary defects



Panel A. The presence of APA (P<0.0001) and their titers (P= 0.008) were significantly associated with the number of pituitary defects

Panel B. The presence of AHA was significantly associated with the number of pituitary defects (P= 0.038), but not with their titer's level (P=0.145)

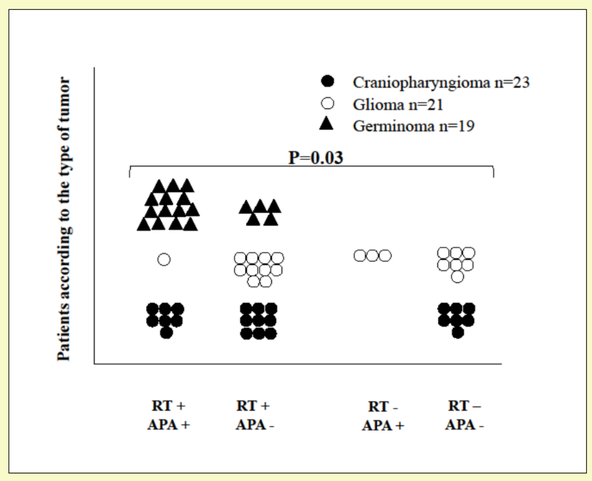
Patients with craniopharyngioma were positive for at least one antibody in 39.1% compared to 33.3% of patients with glioma and to 78.9 % of those with germinoma with similar distributions for APA and AHA between the three tumors (Table 2). The presence of APA or AHA and of both APA and AHA was significantly increased in patients with germinoma **(Table 2).**

Table 2. Distribution of APA and AHA based on the type of tumor

	Ab n=31 [a]	APA n=25 [b]	AHA n=26 [c]	APA/AHA n=20 [d]
Craniopharyngiomas (n=23)	9 (29.0)	7 (28.0)	7 (26.9)	5 (21.7)
Gliomas (n=21)	7 (22.6)	4 (16.0)	5 (19.2)	2 (9.5)
Germinomas (n=19)	15 (48.4)	14 (56.0)	14 (53.9)	13 (68.4)

Ab = At least one antibody positive
APA = only APA positive
AHA= only AHA positive
APA/AHA = both APA and AHA positive
[a] p = 0.007; [b] p = 0.001; [c] p = 0.002; [d] p = < 0.001

Fig 3. Distribution of 63 patients with brain tumors based on tumor type, presence of APA and radiotherapy. APA and radiotherapy were significantly associated (P=0.03)



CONCLUSIONS

Patients with brain tumors and in particular germinoma, develop an autoimmune reactions involving the hypothalamic-pituitary region that may contributes to endocrine dysfunction.
Attention should be paid to avoid missing the diagnosis of germinomas masked by an Autoimmune pituitary condition.

References

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