Acta Pathol. Jpn. 32(6): 925~931, 1982

PITUITARY-ADRENAL AXIS IN PINEALOMA

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Autopsy series of 19 patients with pineal and anterior third ventricle (suprasellar) tumors were analyzed with regard to shift in pituitary-adrenal axis. Germinomas formed the most common subgroup in this series (79%). Metastatic tumor growth in the pituitary gland caused adrenal atrophy in 4 cases. Some patients with pineal neoplasms had larger adrenals in weight compared with age- and sex-matched controls of Japanese. In three patients with sexual precocity, adrenal weight was larger. It is concluded that clinical importance exists in anterior pituitary insufficiency with adrenal atrophy, but hyperfunction of the hypophyseoadrenal system might occur during the course of the disease. ACTA PATHOL. JPN. 32: 925~931, 1982.

Introduction

Human pineal seems to be one of the vestigial organs from the viewpoint of vertebrate orthogenesis, because in the phylogenetically advanced animals the structures for visual perception tend to decrease in quantity and in quality.[3,17] However, the human pineal organ has a very rich capillary net-work in the interstitial tissue and has sophisticatedly differentiated pinealocytes in the parenchymal lobules[22], the appearance of which can be shown distinctly by del Rio-Hortega's method.[7] Morphological survey on pineal phylogeny[16] strongly suggests that the pineal is a sense organ in the lower vertebrate, e.g. parietal eye of lizard, and has an endocrine or neuroendocrine function in the higher animals.

Since HEUBNER reported precocious puberty in a pinealoma case,[12] much work has being done on the pineal-gonadal axis by biologists and others.[20] Animal experiments have suggested the role of the pineal in the regulation of the other organs of internal secretion.[11,19] Recently, we investigated the relationship between pineal and adrenal cortex morphometrically.[10]

The aim of this paper is to estimate the tendency to adrenal weight change in the patients died of pineal region tumors, and to speculate the possible mechanism of its endocrine manifestations.

Patients and Method

Clinical and autopsy protocols, and microscopic sections were reviewed of 24 patients who died of pineal and suprasellar neoplasms from 1955 to 1977, with special interest in adrenal weight.

Accepted for publication December 25, 1981.

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Because autopsy had been limited in a brain examination in five cases, 19 cases were analyzed in this study. The male-to-female ratio was 5.3/1 (16/3). The age- and sex-matched control value of adrenal weight was founded on the reference (AIMI, S. *et al.* 1952). Tumors were retrospectively classified according to RUBINSTEIN's criteria.[21]

I. Tumors of Germ Cell Origin:
   1. Germinoma (Atypical pineal teratoma; pinealoma)
   2. Teratoma
   3. Choriocarcinoma
   4. Embryonal Carcinoma

II. Tumors of the Pineal Parenchyma:
   1. Pineocytoma
   2. Pineoblastoma (medulloblastoma pinealis)
   3. Ganglioneuroma and Ganglioglioma

III. Other Neoplasms of the Pineal Region:

Results

1. Incidence of pineal region tumors in TP autopsy series.

During the past 22 years, there were 24 autopsy cases of pineal region tumors in our department, which constitute 0.2% of all the autopsies (ca. 11,000), 11% of all the brain and meningeal tumor cases (223), and also 18% of the intracranial tumors between the age of 0 and 35 years (137). Age-related incidence of pineal region tumor in brain tumor death was as follows; 12% of the intracranial tumors in 0–4 years old, 10% in 5–9 years old, 22% in 10–14 years old, 21% in 15–19 years old, 32% in 20–29 years old and 10% in 30–35 years old.

2. Adrenal weight change in pinealoma.

Nineteen cases of pineal and suprasellar region tumors are outlined in **Table 1**. Germinomas formed the most common subgroup in this series (79%).

As an indicator of adrenal weight change, we used the ratio of adrenal weight/control value (A/B). Nine cases (47%) showed over 20% increase in adrenal weight, five (26%) within a range of ±20%, and five (26%) over 20% decrease. Figure 1 shows the histogram of A/B value (median 1.15).

There were 7 cases, in which glucocorticoid was not prescribed before death and the pituitary gland was verified to be intact at autopsy. In this group, two cases of pineal tumor (Cases 1, 9) had A/B value of 1.2 and 1.5, three cases of suprasellar tumor (Cases 3, 7, 8) 3.7, 1.5, and 1.0. In two cases with apparently independent tumor growth found in the pineal and in the anterior third ventricle (Cases 6, 11), the A/B ratio was 2.0 and 1.3.

Cases with pituitary invasion by tumor showed marked decrease in adrenal weight (Cases 10, 14, 15, 16) with the exception of Case 17 (**Table 1**, Figs. 1 & 2).

Histological examination of the adrenals revealed solitary adenoma in Cases 5 and 6, and nodular hyperplasia of the cortex in Cases 19(+), 11 (±), and 12 (±). Marked atrophy of the adrenal cortex was found in Cases 1, 2, and 14. Paraffin-embedded blocks of the adrenals had been scattered and lost in Case 3.

Table 1. *TP Autopsy Series of 19 Patients with Pineal and Suprasellar Tumors. Sexual precocity occurred in 3 patients (Cases 3, 6, 11).*

No.	Age Sex	Tumor Location: Supra-sellar	Tumor Location: Pineal	Histology of Tumor	Pituitary Involvement by Tumor	Predonine Treatment	Bilateral Adrenals (gram, A)	Control Value (gram, B)	A/B
1.	1 M		■	Pineoblastoma			4.5	3.8	1.18
2.	2 F	■		Pineoblastoma	infarct	○	4.3	3.5	1.23
3.	7 M	■		Teratoma			11.0	3.0	3.67
4.	7 M		■	Embryonal carcinoma		○	8.0	3.7	2.16
5.	7 F	■		Germinoma		○	2.7	3.5	0.77
6.	11 M	■	■	Germinoma			12.0	6.1	1.97
7.	12 M	■		Germinoma			9.3	6.2	1.50
8.	12 M	■		Germinoma			6.0	6.1	0.98
9.	13 M		■	Germinoma			16.0	10.7◀	1.50
10.	14 F	■		Germinoma	○		2.5	6.9	0.36
11.	16 M	■	■	Germinoma			10.0	7.5	1.33
12.	18 M		■	Germinoma		○	8.0	9.4	0.85
13.	19 M	■		Germinoma		○	15.1	11.3	1.34
14.	21 M	■	■	Germinoma	○	○	7.5	11.5	0.65
15.	24 M	■	■	Germinoma	○	ACTH	3.8	11.5	0.33
16.	27 M	■	■	Germinoma	○		6.0	10.7	0.56
17.	28 M	■	■	Germinoma	○		14.5	10.7	1.36
18.	29 M	■		Germinoma		○	10.0	10.7	0.93
19.	31 M		■	Germinoma		○	11.0	11.5	0.96

◀ : [*sic*]

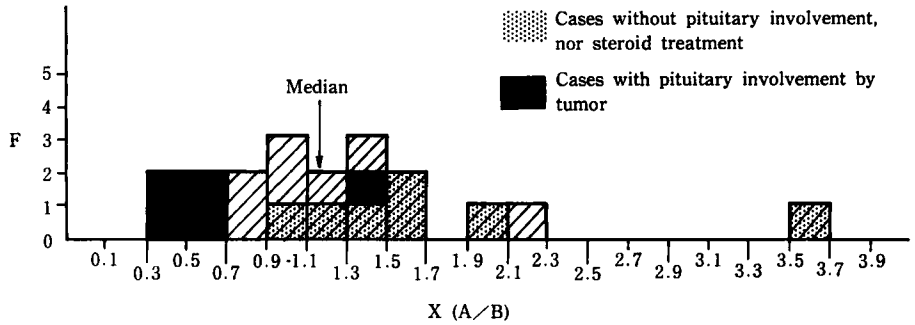

Fig. 1. Distribution of adrenal weight change index (A/B) in patients with pineal and suprasellar neoplasms.

3. *Relation of adrenal weight change to other factors.*

The cerebrospinal fluid (CSF) was examined in 13 patients clinically. In this series, no significant relation was found between the initial pressure of lumbar puncture (mm H_2O) and the index of adrenal weight change (A/B; r=–0.12, N=13).

The duration of disease in 19 patients was 30 months in average and 17 months in median. Individual length of duration (months) appeared to be unrelated to change in adrenal weight (A/B; r=0.12, N=19).

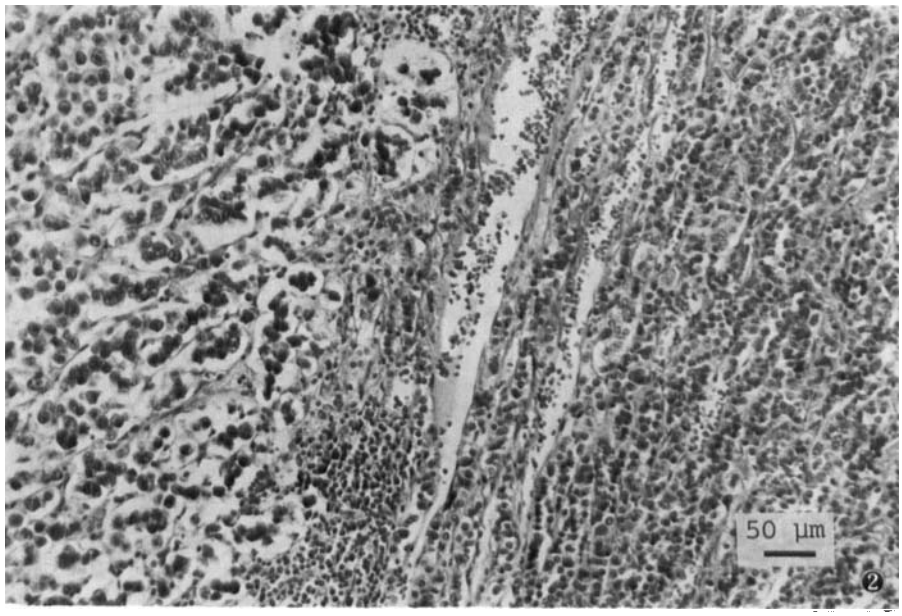

Fig. 2. Suprasellar germinoma. Infiltration in the anterior pituitary (case 10). H.E. stain. Original magnification × 100.

4. Sexual precocity in pineal tumors.

Abnormal maturation of the reproductive system is among the most well-known endocrine manifestations of pineal tumors[2], possibly relating to the anterior pituitary function. In the present series, *sexual precocity* occurred in 3 male patients (Cases 3, 6, 11) with A/B value of 3.67, 1.97, 1.33. One of these patients showed elevated urinary excretion of gonadotropin (Case 11). Precocious puberty occurred solely in those with nonparenchymal tumors in this series, including typical and atypical teratomas, and not in those with parenchymal pineoblastoma (pineal medulloblastoma). The pituitary gland was not involved by tumor histologically and there were no clinical history of glucocorticoid treatment in those with sexual precocity. Curiously enough, combined lesions in the pineal region and in the anterior third ventricle were shown in two patients with germinoma (Cases 6, 11).

Discussion

In this study, the patients with pineal and suprasellar tumors presented increase in adrenal weight, when the pituitary – adrenal axis had been free from the major influential factors such as direct invasion of tumor, or extrinsic steroid treatment. Judging from the fact that these patients suffered from a disease of rather long duration, we believe it is rational to correlate adrenal weight change with the existence of the neoplasm. We could not detect any evidence suggesting the relationship between increase in intracranial pressure and adrenal weight change.

We found 3 cases of precocious puberty among 11 patients under the age of 16 years (27%). All were in males. Hypothalamic involvement by the pineal tumors did not exclude the occurrence of abnormal sexual development, but destructive tumor growth in the pituitary gland deprived of this possibility. KITAY and ALTSCHULE reviewed the literature and found sexual precocity in 26% of the pineal tumors from 1 to 16 years old.[14,15].

It is interesting to compare the present results in man with the recent data about the experimental pineal tumors induced by intracerebral inoculation with JC virus (JCV), a human polyoma virus[24]. Concerning the pathophysiological effects of the virus -induced pineocytomas in hamsters, QUAY demonstrated[18] that the small parenchymal tumors of the pineal resulted in significant reduction in pituitary and ovarian weights, but no or only slight increase in adrenal weights (not significant).

Under physiological conditions the pineal exerts an inhibitory influence on gonads,[20] thyroid[13] and adrenals[25] in rodent species. So it is possible that the parenchymal tumors originating in the pineal gland do produce the pineal antigonadotropic and other principles, e.g. melatonin, in some cases[4]. On the contrary, the non-parenchymal teratomas in the pineal and suprasellar regions can promote the secretion of the releasing factors (RF, or RH) from the hypothalamic nuclei, either secondarily to a decreased pineal secretion of a hypothalamotropic hormone or pressure of the hypothalamic centers.

As a matter of course, direct invasion or metastasis to the pituitary resulted in adrenal atrophy (Fig. 1). In this study, pituitary involvement by tumor was histologically shown in 5 patients of total 19 cases (26%). It is worthy of note that anterior pituitary insufficiency with adrenal atrophy is life threatening in patients with pinealoma. If there are symptoms and signs of adrenal insufficiency, it is advisable to consider the possibility of pituitary involvement by the tumor first and to try the patient with glucocorticoid.

The most common group of pineal neoplasms in Japan are said to be the germinomas (atypical teratomas); they represent 79% of the cases in TP autopsy series. DE GIROLAMI and SCHMIDEK reported a series of 53 cases of pineal region tumors, 35 pathologically verified ones, at the Mass. General Hospital[6], in which 40% of tumors were germinomas (14/35 cases). Tumors of pineal parenchymal cells are very rare, 11% in our series (2/19 cases) and 23% in MGH series (8/35 cases). From these results that at least 70% of pineal region tumors are germinomas, which are generally accepted as highly radiosensitive[5,23], the joint efforts between neurosurgeons, neuroradiologists, radiation therapeutists and pathologists are essential to control the pineal neoplasms especially in Japan.

Does a pinealoma have a capability to synthesize melatonin and other pineal principles? WURTMAN *et al.* (1966) demonstrated HIOMT activity, melatonin producing enzyme, in a suprasellar germinoma. BARBER *et al.* (1978) reported the elevated serum level of mid-day melatonin in 5 radiologically diagnosed pinealoma cases. In animal experiments, pinealectomy resulted in hypertrophy of the adrenal

cortex and melatonin administration resulted in atrophy in lizard[9], in rat[8,13] and in mice.[25] So, we hypothesized that melatonin-producing pinealoma might cause adrenal atrophy in man. As shown above, most cases of the pineal tumors in the present series were non-parenchymatous teratomas and rather had an opposite effect on adrenal weight.

In this study, we came to a conclusion that most germinomas seem to be non-functioning as a hormone producer, but have a potential to cause sexual precocity and adrenal weight change. In order to clarify the mechanism of these endocrine manifestations, it is most important to correlate prospectively the anatomy of tumor extension in the brain with clinical and pathological data in each case.

Acknowledgement: This work was supported in part by a Grant-in-aid from the Ministry of Education, Science and Culture of Japan. Thanks are due to Prof. Y. URANO, Department of Pathology, Kobe University School of Medicine for suggestions and criticisms of the manuscript.

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