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# Pineal gland in old age; quantitative and qualitative morphological study of 168 human autopsy cases

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Age-related changes of human pineal gland were studied morphologically on 168 autopsy cases. Pineal weight in the formalin-fixed condition was 99 ± 56 mg in males ($n$ = 88, mean age 78 years) and 91 ± 41 mg in females ($n$ = 80, mean age 79 years), which showed no sexual difference ($P$ = 0.290). There was no correlation between pineal weight and age of the patient ($r$ = –0.0678, $P$ = 0.191, $n$ = 168). The pineal volume calculated as a spheroid was directly proportional to the weight ($r$ = 0.904, $n$ = 167, $P$ = 0.000). A significant correlation existed between pineal weight and the degree of calcification ($r$ = 0.231, $P$ = 0.002, $n$ = 156). The density of the pineals decreased with age ($r$ = –0.164, $P$ = 0.017, $n$ = 167). The degree of calcification and cyst formation did not increase with age, but the grade of cyst formation was related to the pineal volume ($P$ = 0.0002). Some pineals of the patients over 90 years old showed no calcification and appeared indistinguishable from the ones of the younger subjects. The weight and volume of the pineals of the patients with hypertension was appreciably greater than those of the non-hypertensive patients. These results indicate that human pineals do not necessarily degenerate progressively after involution.

## INTRODUCTION

Ontogenetically, the pineal gland of the vertebrates originated from the posterior wall of the third ventricle, and situates between the habenular and the posterior commisure[9]. Recent advances in experimental pinealogy have elucidated multifunctional aspects of this neuroendocrine organ in mammals[20,29], which tranduces the neuronal inputs to the secretion of the pineal principles, especially melatonin, and its age-related changes of the secretory activity[8,18,25].

The human pineal body is a solid, parenchymatous and cone-shaped organ, weighing about 50–150 mg in the adult. In human pineals, calcification, gliosis and cyst formation are so common that this organ is widely and dimly believed to be destined to involute after puberty and to degenerate progressively with advancing age, or suspected to be phylogenetically a rudimentary organ. About 30 years ago, Arieti foresightedly examined 50 human pineal glands in senility and indicated that the pineal maintained its function in advanced age[1]. But by morphological approaches it remains difficult to interprete the functional state of the human pineals. With the new basic research strategy, we investigated 168 human pineal glands in old age to gain the baseline data of their age-related changes.

## MATERIALS AND METHODS

A total of 168 consecutive human autopsy cases (49–97 years old, mean age 78 years) dying of diseases of every kind and of aging were studied morphologically and statistically. They consisted of 88 males (mean age 77.5 years) and 80 females (mean age 79.4 years), which had been accumulated in the Department of Pathology (chief Dr. H. Shimada),

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Tokyo Metropolitan Geriatric Hospital, over a recent period of 1 year. In each case adequate clinical and pathological records were available.

The brains were fixed in 10% formalin solution at autopsy. The weight of the brain including the cerebellum and brainstem was 1232 ± 134 g ($n$ = 163) and showed negative correlation with age ($r$ = −0.344, $P$ = 0.000). The pineal gland was resected from the brain about one month later and the arachnoidal tissue covering the gland was removed carefully. After leaving it on a filter paper for a while, the weight of the pineal gland was measured by a direct reading balance (Mettler H20, sensitivity 0.01 mg) as well as the length (2a), width (2b) and thickness (2c) were by a slide caliper (sensitivity 0.1 mm). Then the volume of the gland was estimated by calculation, considering it as a spheroid body (4/3 $\pi$ abc). After measurements, the gland was transected with a clean blade longitudinally into two halves or 3 parts.

The grade of the cyst formation was determined; (Grade 3: macroscopically obvious cyst, the diameter of the cyst was more than ca 2 mm, Grade 2: histologically obvious cyst, the diameter was less than 2 mm, Grade 1: cyst not found). The calcified glands were decalcified in 10% folic acid solution with ion exchange resin (Amberlite IR-120). The paraffin-embedded sections of the pineal gland, cut into 3 $\mu$m slices, were stained with hematoxylin and eosin, Azan–Mallory's, Watanabe's silver impregnation and Congo-red.

The grade of the calcification was morphometrically determined by point counting method at 4 different fields of the parenchyma of each gland, including areas with maximum and minimum calcium deposit, using Reichert's Visopan projection system at objective magnification of ×10; (Grade 1: 0–1/100 points; Grade 2: 2–10/100 points; Grade 3: 11–20/100 points; Grade 4: 21–50/100 points; Grade 5: 51–/100 points).

The formalin-fixed adrenal glands from the same group of the patients were also examined. The morphometry of the thickness of the adrenal cortices was performed after routine processing of embedding, sectioning and staining (hematoxylin and eosin, Watanabe's silver impregnation and Azan–Mallory's). Thickness of each zone of the cortex was determined at a magnification of ×100 by means of an eyepiece micrometer. The measured values of 5 different fields were expressed as a mean.

Results consisting of many indices about pineal glands, adrenals and other organs, including a number of malignancies and Kaup index (g, b. wt./cm$^2$, body length), which had been obtained at autopsy, maximum values of serum enzyme activities (GOT, GPT), systolic blood pressure, and history of steroid treatment before death were recorded in the 32 bit minicomputer system (VAX11/750) using interactive database Datatrieve[3]. SPSS-X release 2.1 (operating system: VAX/VMS V.4.1) was used for statistical analysis; frequencies, crosstabs, breakdown, $t$-test, ANOVA, scattergram, Pearson corr, regression[22].

## RESULTS

### *Measurement of the pineal gland in old age*

The weight of the pineal gland in the formalin-fixed condition was 95 ± 49 mg in the present series (mean ± SD, $n$ = 168, median weight 85 mg, skewness = 1.77), 99 ± 56 mg in the male ($n$ = 88, mean age 78 years) and 91 ± 41 mg in the female ($n$ = 80, mean age 79 years), showing no sexual difference by Student's $t$-test ($P$ = 0.290). The maximum weight of the gland was 346 mg and the minimum was 18 mg. Fig. 1 shows the frequency distribution of the base-10-logarithm-transformed pineal weights (mg, skewness = −0.054).

There were no statistically significant correlations between the pineal weight and the age ($r$ = −0.0678, $P$ = 0.191, $n$ = 168) and the pineal volume and the age ($r$ = −0.0014, $P$ = 0.493, $n$ = 167). Table I shows the breakdown of the human pineal weight in old age with means and standard deviation, where the statistical difference was not found between each group by ANOVA (degree of freedom = 4, $F$ = 1.36, $P$ = 0.252). The log-transformed pineal weights also did not show age-related difference (df = 4, $F$ = 1.10, $P$ = 0.359).

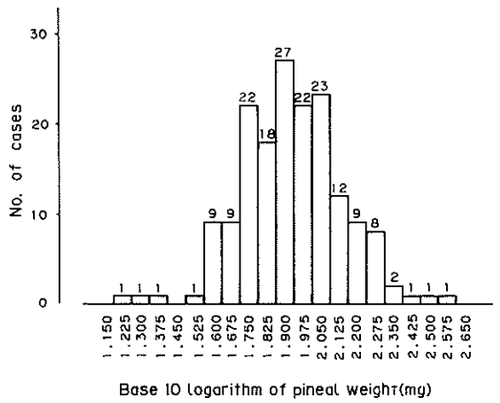


Fig. 1. Frequency distribution of log-transformed pineal weights (mean = 1.928, SD = 0.210, median = 1.929, skewness = −0.054).

TABLE I

*Age-related changes of weight of the human pineal gland (mean ± S.D.)*

| *Age* | *Mean (mg)* | *SD* | *No. of patients* |
|---|---|---|---|
| −70 years | 94.3 | 49.6 | 26 |
| male | 94.7 | 48.9 | 17 |
| female | 93.6 | 53.9 | 9 |
| 71–75 years | 99.1 | 48.5 | 34 |
| male | 98.4 | 57.2 | 17 |
| female | 99.9 | 39.9 | 17 |
| 76–80 years | 105.3 | 60.5 | 40 |
| male | 117.0 | 73.8 | 22 |
| female | 90.9 | 35.3 | 18 |
| 81–90 years | 84.5 | 37.7 | 52 |
| male | 87.7 | 38.2 | 24 |
| female | 81.8 | 37.8 | 28 |
| 91 years– | 98.4 | 52.1 | 16 |
| male | 94.9 | 54.2 | 8 |
| female | 101.9 | 53.4 | 8 |
| Total | 95.2 | 49.3 | 168 |

TABLE II

*Age-related changes of the ratio of pineal weight (mg) to total brain weight (g) (mean ± SD)*

| *Age* | *Mean* | *SD* | *No. of patients* |
|---|---|---|---|
| −70 years | 0.0735 | 0.0403 | 26 |
| male | 0.0706 | 0.0384 | 17 |
| female | 0.0789 | 0.0453 | 9 |
| 71–75 years | 0.0798 | 0.0423 | 33 |
| male | 0.0764 | 0.0506 | 17 |
| female | 0.0833 | 0.0327 | 16 |
| 76–80 years | 0.0854 | 0.0460 | 39 |
| male | 0.0912 | 0.0546 | 22 |
| female | 0.0779 | 0.0318 | 17 |
| 81–90 years | 0.0707 | 0.0314 | 51 |
| male | 0.0694 | 0.0291 | 23 |
| female | 0.0717 | 0.0337 | 28 |
| 91 years– | 0.0822 | 0.0467 | 14 |
| male | 0.0785 | 0.0501 | 7 |
| female | 0.0860 | 0.0466 | 7 |
| Total | 0.0775 | 0.0402 | 163 |



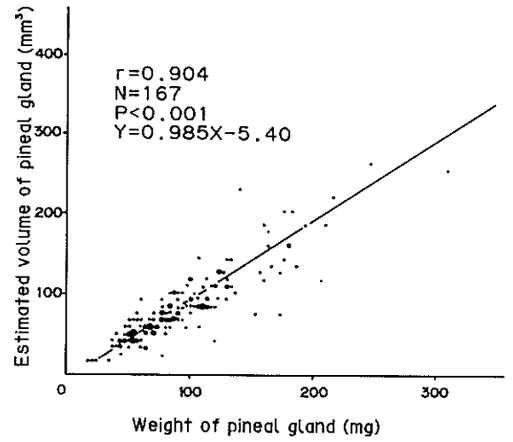


Fig. 2. Relationship between weight and estimated volume of human pineal gland.

The ratio of the pineal weight (mg) to total brain weight (g) was 0.0775 ± 0.0402 in average and was not related to age ($r$ = −0.0302, $P$ = 0.351, $n$ = 163). Table II shows the ratio of pineal weight to total brain weight according to age with breakdown (df = 4, $F$ = 0.882, $P$ = 0.476).

The weight of the pineal gland was directly proportional to the estimated volume ($r$ = 0.904, $P$ = 0.000, $n$ = 167), even if ignoring the influence of the calcification and the cyst formation found in many glands used in this study (Fig. 2). Regression line was $Y$ = 0.985$X$−5.40 ($X$ mg, $Y$ mm$^3$).

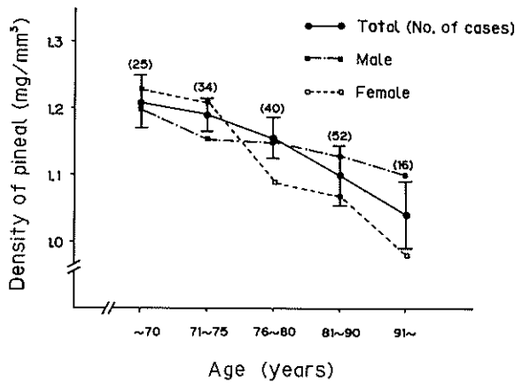


Fig. 3. Age-related change of density of the pineal gland. The means (dots) ± SD (bars) of pineal weights of both sexes ($n$ = 167) are shown as well as means of each sex.

A significant correlation existed between weight density of the pineal gland and age by Peason corr ($r = -0.164$, $n = 167$, $P = 0.017$). Fig. 3 shows age-related decreases of weight density of the pineal gland (mg/mm$^3$). The linearity was significant (df = 1, $F = 5.31$, $P = 0.0225$), but statistically the difference between each group was not significant by ANOVA (df = 4, $F = 1.36$, $P = 0.251$).

*Connective tissue framework of the pineal gland*

The connective tissues arise from the capsule and extend into the pineal parenchyma with capillaries, forming the lobular architecture. In most pineals in this series, the vascular stroma formed the fibrous trabeculae of various thicknesses (pseudoalveolar pattern) as shown by silver impregnation. Cytologically, pineal parenchymal cells did not show atrophy, nor did hyperplastic signs.

*Calcification (acervuli, corpora arenacea) and cyst formation of the pineal gland*

Tables III and IV show the result of the morphometrical study investigating the relationships of the degree of calcification of the pineal gland to age and to pineal weight, both of which were not statistically significant by Chi-square test ($P = 0.971$ and $P = 0.164$, respectively), but there was a trend toward an increase of pineal weight with an increase of calcium deposition. A significant correlation existed between pineal weight and extent of calcification by Pearson's correlation test ($r = 0.231$, $P = 0.002$, $n = 156$). Calcium deposition of above 2/100 points in the histometrical study (Grade 2–5) was found in 65% of the subjects in the Low-75 years age group, 62% in the 76–85 years age group and 68% in the 86-High years age group (Table III).

TABLE III

*Relationship between the degree of calcification of the pineal gland and age (Chi square = 0.525, P = 0.971)*

| *Extent of calcification* | *Age* | | | *Total* |
|---|---|---|---|---|
| | *—75 years* | *76–85* | *86 years–* | |
| 0– 1/100 | 19 | 25 | 12 | 56 (35.9) |
| 2–10/100 | 18 | 21 | 14 | 53 (34.0) |
| 11– /100 | 17 | 19 | 11 | 47 (30.1) |
| Total | 54 (34.6) | 65 (41.7) | 37 (23.7) | 156 (100.0) |

TABLE IV

*Relationship between the degree of calcification and the weight of pineal gland (Chi square = 6.52, P = 0.164)*

| *Extent of calcification* | *Weight of pineal gland* | | | *Total* |
|---|---|---|---|---|
| | *–70 mg* | *70–100 mg* | *100 mg–* | |
| 0– 1/100 | 24 | 18 | 14 | 56 (35.9) |
| 2–10/100 | 18 | 16 | 19 | 53 (34.0) |
| 11– /100 | 13 | 11 | 23 | 47 (30.1) |
| Total | 55 (35.3) | 45 (28.8) | 56 (35.9) | 156 (100.0) |

Cysts of various dimensions, from microscopical to 0.5 × 0.3 × 0.2 cm in size, were observed in the pineals. They existed almost always adjacent to the loose glial scars (neuroglial plaques). Tables V and VI show the relations of the cyst formation to the age and to the pineal weight. The glial cyst formation was more prominent in the glands of heavy weight ($P = 0.0002$) and was not correlated with age ($P = 0.926$). A significant correlation existed between pineal weight and degree of cyst formation by Pearson's test ($r = 0.442$, $P = 0.000$, $n = 156$).

Three out of 16 patients over 90 years old had the pineal gland with very slight or no calcification (Grade 1) and without cyst formation (Grade 1). These glands were rather light in weight (18, 40 and 79 mg). In 3 out of 16 patients over 90 years old, the pineal showed severe calcification (Grade 4) with pineal weight of 54, 106 and 178 mg.

*Pineal gland and malignancy*

Experimental studies have suggested that pineal activity can possibly affect the growth and metastasis of some tumors directly, or indirectly[2,11]. In this study, there were 78 patients who had been shown at

TABLE V

*Relationship between the grade of cyst formation of pineal gland and age (Chi square = 0.894, P = 0.926)*

| *Grade of cyst formation* | *Age* | | | *Total* |
|---|---|---|---|---|
| | *–75 years* | *76–85* | *86 years–* | |
| 1. No cyst | 30 | 40 | 24 | 94 (60.3) |
| 2. Microscopic | 11 | 11 | 6 | 28 (17.9) |
| 3. Macroscopic | 13 | 14 | 7 | 34 (21.8) |
| Total | 54 (34.6) | 65 (41.7) | 37 (23.7) | 156 (100.0) |



TABLE VI

*Relationship between grade of cyst formation and weight of pineal gland (Chi square = 22.6, P = 0.0002)*

| *Grade of cyst formation* | *Weight of pineal gland* | | | *Total* |
|---|---|---|---|---|
| | *–70 mg* | *70–100 mg* | *100 mg–* | |
| 1. No cyst | 42 | 30 | 22 | 94 (60.3) |
| 2. Microscopic | 9 | 8 | 11 | 28 (17.9) |
| 3. Macroscopic | 4 | 7 | 23 | 34 (21.8) |
| Total | 55 (35.3) | 45 (28.8) | 56 (35.9) | 156 (100.0) |

autopsy to have malignant tumors of various kinds including clinically latent ones. The pineal gland of these patients weighed 91 ± 46 mg (mean ± SD) and the pineals of the patients without malignancy ($n = 90$) weighed 98 ± 53 mg, which showed no difference ($t = 0.920$, $P = 0.361$). The log-transformed pineal weight of the former group was 1.91 ± 0.20 (mean ± SD) and of the latter group was 1.93 ± 0.23 ($t = 0.630$, $P = 0.531$). Tumors metastatic to the pineals are sometimes encountered in the autopsy cases with malignancy[14,26]. No such patients existed in this series.

The Kaup index (body weight/body length$^2$) was used here to estimate the nutritional state. A decrease in the Kaup index occurred according to age ($r = -0.124$, $P = 0.061$), but no relationship was found between pineal weight and Kaup index ($r = -0.0068$, $P = 0.467$).

*Pineal gland and blood pressure*

The weight of the pineal in hypertensive patients with systolic pressure of over 150 mm Hg before death was 107 ± 59 mg ($n = 44$) and slightly heavier than that in non-hypertensive patients (91 ± 45 mg, $n = 124$), but this difference was not significant by $t$-test ($P = 0.064$). The log-transformed pineal weight of the former group was 1.97 ± 0.23 and of the latter group was 1.91 ± 0.20, which also showed no statistically significant difference ($t = 1.59$, $P = 0.113$). The estimated volume of the pineal in hypertensive subjects (103 ± 71 mm$^3$) was significantly larger than that in non-hypertensive patients by $t$-test (84 ± 45 mm$^3$, $P = 0.045$).

The patient with the heavy heart was suspected to have been hypertensive. The weight of the pineals from the patients with heart weight of more than 400 g was 91 ± 36 mg ($n = 32$) and from others was 96 ± 52 mg ($n = 136$). This difference was not significant by Student's $t$-test ($P = 0.58$).

No significant relations existed between pineal weight and systolic pressure ($r = 0.0966$, $P = 0.150$, $n = 117$) and pineal weight and heart weight ($r = -0.0246$, $P = 0.379$, $n = 161$). A significant negative correlation existed between systolic pressure and extent of calcification of the pineal gland ($r = -0.214$, $n = 108$, $P = 0.013$). There was no relationship between weight of the heart and degree of calcification of the pineal gland ($r = 0.0819$, $n = 149$, $P = 0.160$).

We could not get any reliable data about the premortem chronic use of antihypertensive drugs such as $\beta$-blockers.

*Pineal gland in endocrine environment*

The multifunction of the pineal gland in the regulation of the endocrine organs in the mammalian body ('a regulator of regulator') has been studied recently by many workers[20]. There was no relationship between pineal weight and pituitary weight ($r = -0.048$), thyroid weight ($r = 0.052$) and adrenal weight ($r = 0.096$). Many attempts have been also made on humans to elucidate the pineal-adrenal cortex relationship in normal and disease[5,6,7,27]. In the present series, no significant correlation was found between pineal weight and the thickness of the three layers of the adrenal cortex ($r = -0.089$ to $-0.022$).

*Other pathological phenomena in the pineals*

Slight perivascular chronic lymphoid cell infiltration was found focally in the two pineals. No granulomatous lesion existed in the pineals, nor did amyloid angiopathy and microabscesses in the present series.

Many pineals showed severe arteriosclerotic change in the capsule and the stromal capillaries, causing an increase in the thickness of the vascular wall with hyalinous degeneration.

The deposition of the brownish yellow pigments in the connective tissue stroma of the pineal gland took place in 7 cases (mean age 77, range 69–85 years), which had probably occurred after extravasation of erythrocytes.

## DISCUSSION

Although the physiological significance of the human pineal gland is uncertain, more and more work-

ers speculate this organ to have some endocrine functions in humans as well[12,21,29]. In recent years it has been demonstrated that human pineals synthesize melatonin accompanied with changes in serum[28], plasma[15] and urinary[10] melatonin levels. If we clarify the age-related changes and pathological findings of the human pineal gland, the clue to the unknown function of the human pineal gland may be found. From this viewpoint, we performed quantitative and qualitative histological studies of the human pineal gland to gain the baseline data concerning their age-related structural changes and analyzed the data statistically.

Pineal weight did not differ in males and females in this study (mean weight; 99 mg in male, 91 mg in female). The mean comparable figures of the pineal gland in Arieti's series were 148.5 mg in males and 126.5 mg in females[1], and in Tapp's series 174 mg in 75–90 years-old age group in males and 214 mg in 75–90 years-old age group in females[24]. Meanwhile, the mean weight of the brain was 1232 g in the present series and 1243 g in Arieti's series. The ratio of pineal weight to brain weight was $0.775 \times 10^{-4}$ in average (1/12,900) in the present series, compared with $1.1 \times 10^{-4}$ (1/9000) reported by Arieti[1]. Judging from these and other observations[4], the weight of the human pineal gland in senility seems to be rather lighter in the Japanese than in the people of the western countries, although the difference could be in part attributed to conceivably different techniques of resection, removal of the arachnoidal tissue and fixation.

There was no correlation between pineal weight and age here ($r = -0.0678$) and the adult weight of the pineals was maintained into old age, in accordance with other gravimetric studies[4,19,23]. In this study it is indicated that after involution the human pineals may be stationary in morphology in advanced senility. The histological architecture had a pseudoalveolar pattern and there were no cases which showed a severe decrease in the cellularity of the pinealocytes.

Naturally the weight of the human pineal gland was proportional to the estimated volume ($r = 0.904$). The density of the pineals in the fixed condition showed age-related decrease, from ca 1.2 mg/mm$^3$ to 1.0 mg/mm$^3$. Considering the errors on estimation of the pineal volume, the real density may be a little more larger. Partly the decrease of density seems to depend on the fact reported as increased amount of lipid in old age[16,17].

Despite various hypotheses, the significance of calcareus concretions in the human pineal gland has been controversial[1,23] and it is not clear now whether that finding means degeneration and has some relation to the secretory activity of the human pineals. The degree of calcification, which had been estimated morphometrically, did not increase with age and corpora arenacea of Grade 2–5 (over 2/100 points in the histometry) were found constantly in 60–70% of the 3 age groups (–75 years, 76–85 years, 86 years–) in the present series. Okudera et al. described that the incidence of calcification in the pineal region increases up to the age of 30 years and in people older than 30 years calcification in the pineal region was found in about 70% on computed tomography without increase in proportion to age[13]. Judging from these results, acervuli represents normal pineal involution and the degree of calcification in the pineals may be stationary in advanced senility.

The cause of cyst formation in the human pineals still remains obscure, but it is generally thought that pineal cysts represent an involution. They existed in about 40% of the patients in our series, including macroscopically and microscopically identified ones, and a slightly lower figure (25%) was presented by Tapp and Huxley[24]. The cysts existed almost always adjacent to neuroglial plaques and the cyst formation was more prominent in the pineals of heavier weight in this study, although the causal relationship is unknown. Cyst formation did not appear to be age-dependent in old age statistically. The pineal cysts may have a more significant relation to the velocity of progress of arteriosclerosis than to age itself and may not represent the involutional process in the young adult period.

In the context of the putative control function of the pineal gland as an oncostatic gland[2,11], the morphological changes in the human pineal gland dying of malignant neoplasms have been reported[14,19,26]. In the present results, however, there was no change in the pineal glands associated with malignancy.

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