Incidental Pituitary Lesions in 1,000 Unselected Autopsy Specimens

PURPOSE: To elucidate the frequency of false-positive results in imaging diagnoses of a functioning pituitary microadenoma, the authors studied various kinds of incidental lesions greater than 2 mm in diameter from a larger series of pituitary glands.

MATERIALS AND METHODS: One thousand pituitary glands were studied in a nonselected autopsy series. Most causes of death were acute diseases or accidents. Each gland was fixed in 10% formalin and was then cut horizontally into three or four pieces, which were prepared for usual light microscopy.

RESULTS: Of 178 glands found to have incidental lesions, 61 (34%) lesions were larger than 2 mm. Included were adenomas and hyperplasias (n = 20), Rathke cysts (n = 37), infarctions (n = 2), and hemorrhages (n = 2). Seventeen (74%) of 23 laterally localized lesions were adenomas, and 33 (87%) of 38 medially situated lesions were Rathke cysts. These lesions were found in 5.8–8.3% of subjects in every generation aged 30 years or older.

CONCLUSION: Incidental lesions should be considered a cause of false-positive findings (6.1%) when an imaging diagnosis is made of a functioning pituitary microadenoma.

With the recent development of imaging diagnoses, the detection of a tiny pituitary microadenoma has become possible in patients with hypersecretion of pituitary hormones (1,2). By using accurately calibrated dynamic computed tomography (CT) or magnetic resonance (MR) imaging, a microadenoma of 2–3 mm in diameter can be identified in the pituitary gland.

However, the pituitary gland normally contains various kinds of incidental lesions (eg, microadenomas, Rathke cleft cysts, hematomas, infarctions). Therefore, it is important to know how common these lesions are among the general population when making an imaging diagnosis of a tiny functioning microadenoma (3–6).

Although considerable reports on this subject have been published, most, to our knowledge, have dealt with only one category of lesions of the pituitary gland and were mainly from the epidemiologic or pathologic viewpoints. These articles focus on the prevalence and histologic aspects of a special lesion but not on details regarding the size and location of the abnormality. They rarely discuss other kinds of incidental lesions.

Therefore, these data were not useful for diagnostic radiology because they mixed strictly microscopic lesions with larger ones detectable with modern imaging technology.

To contribute to the imaging diagnosis of tiny functioning microadenomas, we studied the prevalence of various incidental pituitary lesions, especially those larger than 2 mm, and their combinations found in a large group of subjects.

MATERIALS AND METHODS

One thousand pituitary glands obtained from necropsies performed at the Tokyo Metropolitan Medical Examiner's Office during a 3-year period were studied. They were unselected but were not necessarily consecutive cases.

There were 726 male and 274 female autopsied subjects. The number of subjects by age groups was as follows: aged 0–9 years (n = 44), aged 10–19 years (n = 24), aged 20–29 years (n = 91), aged 30–39 years (n = 120), aged 40–49 years (n = 228), aged 50–59 years (n = 186), aged 60–69 years (n = 163), aged 70 years or older (n = 144). Most deaths resulted from acute diseases or accidents: cardiac failure (n = 388), accidents (n = 220), cerebrovascular diseases (n = 138), pneumonia (n = 93), gastroenteric diseases (n = 71), and other causes not related to pituitary lesions (n = 90). According to the autopsy records, no subjects had preexisting pituitary diseases. No hospital deaths were included.

Each pituitary gland was fixed in 10% buffered formalin and was then cut horizontally into three or four pieces. The thickness of each piece ranged from 1.0 to 1.5 mm. These pieces were embedded in paraffin and were sectioned and stained with hematoxylin and eosin in the usual way. When abnormalities were found, serial sections were made until the largest diameter could be obtained.

Twenty glands that contained a microadenoma or a hyperplasia were studied with immunohistochemistry by using the indirect peroxidase method. Antibodies used and their dilution rates were as follows: growth hormone, prolactin, thyroid-stimulating hormone, follicle-stimulating hormone, and luteinizing hormone from the National Institute of Arthritis and Metabolic Diseases (1:500–1,000) and adrenocorticotropic hormone from Tokai University (1:40).

RESULTS

Of 1,000 pituitary glands, 178 (18%) glands contained one or two lesions. Sixty-one (34%) glands had lesions larger than 2 mm (average diameter). Combined lesions were classified as being the larger.
Pituitary adenomas (n = 31) and nodular hyperplasia of adenohypophyseal cells (n = 20) were found. The definition of both lesions was based on that of Burrow et al (7). Adenomas were identified by the following criteria: uniformity of the cells, a stromal pattern that differed from the rest of the gland, and evidence of compression of the adjacent pituitary parenchyma. Similar focal lesions not meeting these criteria were considered to be hyperplasia.

Eighteen adenomas and two hyperplasias were larger than 2 mm. The diameters of these lesions ranged from 2 to 4 mm in 15 subjects and from 4 to 6 mm in five subjects. Seventeen lesions were located in the lateral wings of the gland, and three were situated in the mucoid wedge (Figure, parts a and b).

Two glands contained other lesions, namely, a smaller adenoma (0.5 × 0.5 mm) and a hyperplasia (1.8 × 2.5 mm). A small Rathke cleft cyst was inside the adenoma in two subjects.

All adenomas and hyperplasias were chromophobic with hematoxylin-eosin stain. Immunohistochemically, six adenomas tested positive for prolactin, and 14 lesions tested negative for all anterior pituitary hormones.

These 20 lesions were found in 14 men and 6 women, ranging in age from 40 to 85 years (mean, 58.5 years ± 15.1). The causes of death were as follows: cardiac failure (n = 8), cerebrovascular disease (n = 4), accidents (n = 3), pneumonia (n = 2), and other causes (n = 3). According to the autopsy records, a goiter in two subjects and an ovarian cyst in one were found to be the abnormality in endocrine organs.

Rathke cleft cysts were found in 113 glands. The cyst was characterized by one layer of ciliated cuboidal or columnar epithelium. Thirty-seven cysts were larger than 2 mm. The diameters ranged from 2 to 4 mm in 29 subjects, from 4 to 6 mm in four subjects, and from 6 to 8 mm in four subjects. Thirty-three cysts were located in the center of the gland, and four cysts extended from the pars intermedia to form their main masses in the lateral wings (Figure, parts c and d). The coexistence of a cyst and a smaller adenoma was found in two glands (diameters of adenomas: 1.8 × 1.4 mm and 2.0 × 1.6 mm).

These 37 lesions were found in 30 men and seven women ranging in age from 18 to 86 years (mean, 50.3 years ± 15.1). The causes of death were as follows: cardiac failure (n = 15), accidents (n = 9), cerebrovascular disease (n = 6), pneumonia (n = 3), and other causes (n = 4). There was no mention of endocrine abnormalities in the autopsy records.

Various abnormalities, such as infarction of the anterior gland (n = 6), hemorrhage (n = 6), granular cell myoblastoma (n = 1), and nodular lymphocyte infiltration (n = 1) were found in 14 glands. Two older infarcts and two hemorrhages (an older and a relatively fresh one) were larger than 2 mm. The size of the fresh hemorrhage was 4.3 mm, and the other three lesions ranged from 2 to 4 mm in diameter. Both infarcts were located in the lateral wings, and both hemorrhages were found in the middle of the gland (Figure, parts e and f). Three lesions were found in men in their 50s, and one hemorrhage was seen in a 57-year-old woman. The causes of death were cardiac failure (n = 2) and accidents (n = 2).

Incidental pituitary lesions were
identified in 47 of 726 (6.5%) male and 14 of 274 (5.1%) female subjects. Age distribution and the incidence rate of lesions are shown in the Table. These lesions were found in 5.8%–8.3% of the subjects older than 30 years. In contrast, they were rare in those aged 29 years or younger. Adenomas and other lesions were seen only in the middle-aged or older subjects (> 40 years of age), and Rathke cleft cysts could be found among all age groups.

**DISCUSSION**

Incidental microadenomas have been reported by many authors to be seen with variable frequencies at routine autopsies. However, most of these studies are based on 100–500 pituitary glands (8–12). A larger series of more than 1,000 autopsies was reported by Costello (13), Hardy (14), and McCormick and Halmi (15). The frequencies of microadenomas, as reported in these articles, were 22.5%, 2.7%, and 8.8%, respectively.

The discrepancy between frequencies may be due to the different methods used (especially the thickness of slices of the gland) and the definition of the adenoma. Costello used the same slice thickness as ours but identified very small cell nests (probably immature hyperplasias) with pituitary adenomas. Hardy did not describe the details of the method. McCormick and Halmi had four standardized pieces from each pituitary gland and included tiny microadenomas in their series. We selected the horizontal slices of 1–1.5 mm because it was useful in screening a lesion larger than 2 mm. The incidence of microadenomas was 3.1% in our study, but it increased to 5.1% if nodular hyperplasias were included. All previous investigators used materials from hospital deaths, which might be influenced by various treatments given the patient, such as steroids, anticancer drugs, irradiation. Because our materials were obtained from subjects who died of acute diseases and accidents, more accurate frequencies of incidental pituitary lesions among the general population might be reflected.

Several authors reported the prevalence of microadenomas larger than 2 mm: Burrow et al (7), seven of 120 (5.8%); Muhr et al (16), three of 205 (1.5%); Char et al (17), 35 of 350 (10%); Kontogeorgos et al (18), five of 470 (1.1%; > 3 mm); and Chambers et al (5), 11 of 100 (11%; > 3 mm). However, little information on the size of adenomas was available from the three larger series. In our study, 18 adenomas and two hyperplasias were larger than 2 mm in diameter.

Seventeen (85%) of 20 masses were located in the lateral wings and three (15%) were found in the mucoid wedge. Kontogeorgos et al (18) also reported that 34 (77%) of 44 incidental adenomas were identified in the lateral wings. Kovacs et al (11) showed that all 15 incidental adenomas were localized in the lateral parts of the gland.

It has been reported that Rathke cysts were found in 13%–22% of subjects at routine autopsies (19–21). However, these articles rarely referred to the precise size and location of cysts, maybe because most cysts were microscopic in size and were usually located in the pars intermedia. Chambers et al (5) found six (6%) pars intermedia cysts that were larger than 3 mm in 100 pituitary glands and Muhr et al (16) identified 18 (8.8%) cysts of 1–6 mm among 205 specimens. MacGrath (22) reported that 12 (17%) of 72 incidental pituitary cysts were larger than 2 mm.

In this study, 113 (11.3%) glands contained Rathke cleft cysts. Of these, 37 (33%) cysts were larger than 2 mm. Thirty-three (89%) of these 37 cysts were localized in the center of the gland, and four (11%) cysts extended and formed their main masses in the lateral wings.

Excluding adenomas and Rathke cleft cysts, other incidental lesions larger than 2 mm were very rare. We found two infarcts in the lateral wings and two hemorrhages in the middle portion of the gland. Chambers et al (5) reported that three infarcts (> 3 mm) were detected in 100 autopsy cases. These infarcts and ours were older completed lesions. However, it is not clear whether some hemorrhages occurred around the moribund phase, because one hemorrhage in our series showed a rather fresh appearance.

It has become possible to detect a very tiny microadenoma of 2–3 mm in diameter by using modern MR imaging technology. However, even if an abnormal finding is obtained, it is not certain whether the lesion is causing the hormone excess (2,5). In addition to incidental microadenomas, asymptomatic Rathke cysts may cause false-positive findings, since they are known to have various kinds of appearances at CT or MR imaging (23,24).

Incidental pituitary lesions (> 2 mm) were found in 5.8%–8.3% of subjects in every generation older than 30 years, although they were not always detected at imaging. Prolactinomas tend to develop most frequently around age 30 years, and adenomas with acromegaly or Cushing disease have a peak occurrence in the 4th or 5th decade. The presence of such false-positive cases should be recognized when diagnosing a microadenoma, especially in Cushing disease. Because endocrinologic examinations can barely help distinguish the pituitary lesion from the ectopic one in Cushing syndrome, selective venous sampling may be necessary to confirm the hypersecretion of adrenocorticotropic hormone from the positive lesion in imaging diagnoses (25,26).

In summary, 61 lesions larger than 2 mm were found in 1,000 pituitary glands. Twenty-three lesions were located in the lateral wings, with 17 (74%) being pituitary adenomas. Thirty-eight lesions were located in the center of the gland, with 33 (87%) being Rathke cysts. These incidental lesions should be taken into consideration when making imaging diagnoses of functioning pituitary microadenomas.

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**References**


