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Incidence of Pituitary Necrotic Lesions in Autopsy Material

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Pituitary necrosis is mostly a result of pituitary haemorrhage or infarct. The frequency of pituitary necrosis in the Polish population has not yet been investigated. Hence, the aim of this study was to estimate the incidence of pituitary necrotic lesions in forensic autopsy material and to assess possible correlations of pituitary necrosis with sex, age, other pituitary pathologies, endocrine disorders and atherosclerosis. Serial sections of 100 human pituitary glands stained with hematoxylin-eosin were examined microscopically.

Pituitary necrosis was found in 19 cases (19%), all of them in persons aged > 40 years. The majority of the lesions had relatively large size, occupying 10-50% of the gland. According to family interviews, none of the subjects manifested any clinical symptoms related to pituitary insufficiency, hence all the detected cases can be regarded as subclinical. There was no association of pituitary necrosis occurrence with sex, other pituitary pathologies found upon autopsy, endocrine diseases or cause of death. Only correlations with age and atherosclerosis were statistically significant.

This study has shown that subclinical pituitary necrosis is a relatively frequent phenomenon in elderly persons, probably resulting from age-related deterioration in the vascular status.

Introduction

Partial or total destruction of the pituitary gland can result from ischemia or hemorrhage, both ultimately leading to pituitary necrosis. The most common examples of such process

include Sheehan syndrome, and pituitary apoplexy. In the literature, some confusion exists over the term “pituitary necrosis”: some authors use it exclusively in the context of ischemic events [14], whereas others include both, ischemic and hemorrhagic lesions in the entity termed pituitary apoplexy [1, 2, 12].

Pituitary apoplexy, a life-threatening syndrome with distinct clinical manifestations including headache and neuro-ophthalmological symptoms, resulting from acute hemorrhage or infarction of the pituitary gland [12], can be triggered by a wide range of precipitating factors including shock, head injury, elevation of intracranial pressure, pituitary adenoma, hypertension, diabetes, cardiac surgery and other surgical interventions, dynamic tests of pituitary function, intravascular coagulopathy, anticoagulants, oral contraceptives, radiotherapy, as well as treatment with bromocriptine and Gn-RH agonists [1, 15, 16]. Such “classical” pituitary apoplexy with its severe symptoms can be even a cause of a sudden death [19].

On the other hand, asymptomatic, i.e. subclinical or silent pituitary apoplexy seems to be quite common [11]. Although “classical” pituitary apoplexy is generally regarded as a very rare disease [16], the true incidence of pituitary necrosis including the clinically silent cases has been the subject of only one study [14]. Hence, the aim of the present investigation was to examine pituitary glands obtained during autopsies unrelated to clinically diagnosed pituitary apoplexy in order to investigate the incidence of pituitary necrosis.

Material and Methods

Pituitary glands of 100 subjects (mean age 51.01 yrs, SD=19.90 yrs, range 17-95 yrs; 57 males, 43 females) were obtained upon autopsy at the Department of Forensic Med-

icine, Jagiellonian University Medical College. The material was collected exclusively from autopsies performed immediately after death. The causes of death included suicide (16 cases), fatal injuries (43 cases), cardiovascular failure (17 cases), accidental poisoning (11 cases), and others (drowning – 5 cases, cerebral hemorrhage – 3 cases, freezing – 2 cases, peritonitis – 1 case, aortic aneurysm rupture – 1 case, and DIC – 1 case). During the autopsy, grade of atherosclerosis based on examination of aorta and coronary arteries was evaluated (0 – absent, 1 – mild, 2 – moderate, 3 – advanced). Data concerning the medical history of the subjects were documented on the basis of family interviews.

Formalin-fixed, paraffin-embedded pituitary glands were cut into 8 µm thick serial sections and mounted on slides, 4 sections per slide. From each gland, every 20th slide was routinely stained with hematoxylin and eosin. Sections were examined under Olympus BX50 light microscope. The necrotic foci were classified into four grades according to their relative size: grade 1: <5%; grade 2: 5-10%; grade 3: 10-50%; grade 4: >50% [14].

Statistical analysis (Statistica v. 7.1, StatSoft Inc., Tulsa, OK, USA) included chi-square test, Fischer's exact test and Student's t-test. The value of $p < 0.05$ was considered statistically significant.

Results

Necrotic lesions in the pituitary were found in 19 out of 100 examined cases (Table 1). According to family interviews, none of those subjects had manifested any clinical symptoms related to pituitary insufficiency during their life. All changes were localized in the adenohypophysis. The diameter of pituitary necrotic foci ranged from 2 mm to 10 mm. The majority of the observed necrotic foci had relatively large size (grade 1 – 1 case; grade 2 – 3 cases; grade 3 – 13 cases; grade 4 – 2 cases). Fibrosis replacing or accompanying the necrotic lesions was an inconstant finding – cavities containing a pale material and some necrotic debris were frequently observed.

In 11 cases, necrotic lesions were the only pituitary pathology observed; in 3 cases they were accompanied by pituitary microadenomas, 1-5 mm in diameter (in one case by 2 different adenomas), remaining in contact with the adenomas. In 3 other cases, we found coincidence of necrotic foci and single or multiple Rathke's cleft cysts, 1-3 mm in diameter, also in contact with necrotic lesions. Two pituitary glands showed multiple pathological changes (necrosis, cysts and adenomas). Neither adenomas nor cysts were diagnosed during life. Pituitary necrosis showed, however, no significant association with the mentioned pathologi-

TABLE 1

General characteristics of the study group

	Age (yrs)		Cases with pituitary necrosis (%)
	Mean±SD	Range	
All cases (n=100)	51.0±19.9	17-95	19 (19)
Male (n=57)	48.3±17.8	18-89	12 (21.05)
Female (n=43)	54.6±22.1	17-95	7 (16.28)

TABLE 2

Age of subjects with/without pituitary necrosis

		Age (yrs)	
		Mean±SD	Range
Cases with pituitary necrosis	All cases (n=19)	61.89±12.02*	40-81
	Male (n=12)	58.50±11.49	40-75
	Female (n=7)	67.71±11.35	51-81
Cases without pituitary necrosis	All cases (n=81)	48.46±20.56*	17-95
	Male (n=45)	45.56±18.31	18-89
	Female (n=36)	52.08±22.82	17-95

*difference statistically significant ($p < 0.001$)

TABLE 3

Atherosclerosis in subjects with/without pituitary necrosis

Grade of atherosclerosis	Cases with pituitary necrosis (men, women)	Cases without pituitary necrosis (men, women)
0	1 (1,0)	35 (19,16)
1	3 (2,1)	7 (4,3)
2	6* (4,2)	23 (12,11)
3	9* (5,4)	16 (10,6)

*association between atherosclerosis and pituitary necrosis statistically significant ($p < 0.002$)

cal changes ($p > 0.05$). In four cases, recent hemorrhage (masses of intact or partially hemolysed red blood cells) accompanied necrosis.

There was no association of pituitary necrosis with sex, and cause of death ($p > 0.05$), however, relation with age was statistically significant ($p < 0.001$, Table 2): necrotic lesions were found exclusively in persons over 40 years of age. Significant association was also observed between pituitary necrosis and atherosclerosis ($p < 0.002$): the majority of subjects with necrotic foci had moderate or high grade of atherosclerosis (Table 3).

In 6 cases with pituitary necrosis, the subjects suffered from endocrine disorders diagnosed upon autopsy (nodular enlargement of thyroid – 3 cases, alveolar thyroid adenoma – 1 case, adrenocortical carcinoma and nodular enlargement of thyroid – 1 case, adrenal degeneration with hemorrhage – 1 case), but there was no significant association of pituitary necrosis with any of these diseases.

Discussion

In the studies aimed at examination of the incidence of any pathology, the forensic autopsies can be regarded as a source of material collected from subjects representing the closest approximate to the “healthy” sample of the population. In this context, the incidence of pituitary necrosis found in our material (19%) is surprisingly high, remarkably higher than the relevant values reported in very scarce publications: 3.1% [14], and <1% [16]. These data, however, are not fully comparable with ours: the former authors did not include hemorrhages, while the latter recorded only clinically manifested and diagnosed cases. Even more surprising finding of our study is the fact that in the cases with very large necrotic foci, occupying nearly or over a

half of the gland, none of the subjects manifested any clinical symptoms related to pituitary insufficiency (as far as the family interview data can be trusted), and hence all the detected cases of pituitary necrosis can be regarded as subclinical. It seems therefore that clinically silent ischemic or hemorrhagic events in the pituitary gland are much more frequent than expected and only a small fraction of such events are diagnosed on the basis of clinical manifestations. In fact, this problem has been mentioned by some authors [10, 11, 17].

The presence of 3 cases with Rathke’s cleft cysts accompanied by necrosis and one case with coexisting Rathke’s cleft cyst and adenoma in our relatively small material also seems to contradict the accepted view that such associations are extremely rare [8, 9].

The correlation of pituitary apoplexy with preexisting pituitary adenoma due to hemorrhage into the tumor is widely accepted and the observed incidence of apoplexy in adenomas ranges from 14.4% to 21% [2, 6, 18]. The lack of such association in our study can be explained in two ways. On one hand, the correlation may be valid only for clinically manifested cases (large adenoma and massive hemorrhage) but not for subclinical events, on the other complete destruction of the adenoma by hemorrhage and necrosis can lead to underestimation of the number of cases, in which such coincidence existed. Indeed, remissions of endocrine disorders caused by pituitary adenomas following pituitary apoplexy have been reported [3, 4, 7].

Some bias in the estimation of pituitary necrosis incidence in forensic autopsy material can result from the fact, that pituitary necrosis due to both hemorrhage and ischemia can be triggered by shock or head injury [5, 13]. Hence, this should always be taken under consideration in the victims of fatal accidents. However, autopsy performed shortly after death would reveal in such cases recent lesions. In our material, a recent hemorrhage with intact or partially hemo-

lysed red blood cells was found only in four cases (3 fatal accidents and freezing) and in all of them “fresh” hemorrhage accompanied preexisting necrotic lesions, indicating that even though the hemorrhage could be precipitated by injury or shock, necrotic lesions had already been present in the hypophyseal tissue.

In the present study, pituitary necrotic lesions were significantly associated only with age and advancement of atherosclerosis. Strikingly, in the investigated population sample, pituitary necrosis was observed only in persons over 40 years of age, and the mean age of that group was as high as 62. It is therefore not surprising that necrosis was also associated with atherosclerosis which on the population scale is closely correlated with age.

In conclusion, this study has shown that subclinical pituitary necrosis is a relatively frequent phenomenon in elderly persons, probably resulting at least in part from age-related deterioration in the vascular status.

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