HIGH PREVALENCE RATE OF PITUITARY INCIDENTALOMA: IS IT ASSOCIATED WITH THE AGE-RELATED DECLINE OF THE SEX HORMONES LEVELS ?

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SUMMARY

Incidental pituitary adenoma is the common finding during brain imaging. According to multistep model of pituitary tumourigenesis genetic alterations provide the initiating event that transforms cells while hormones play a role in promoting cell proliferation. Development of pituitary adenoma in a case of excessive hypophysiotrophic hormones production or reduced feedback suppression by target gland hormones emphasizes the importance of hormonal stimulation in pituitary tumourigenesis. Pituitary hyperplasia has been reported in pregnancy, hypothyroidism and conditions such as CRH or GHRH hypersecretion. Moreover, recent study reported one case of gonadotroph macroadenoma and two cases of gonadtroph cells hyperplasia in patients with Klinefelter syndrome probably due to protracted stimulation of gonadotroph cells because of lack of androgen feedback. Significant changes of the hypothalamic-pituitary-gonadal axis occurred with aging. In females, after menopause, estradiol level decreases by 35-fold and estrone levels by 20-fold that results in increased gonadotropins levels. Similarly, FSH, but not LH, level is increased with advancing age in men, too, although the age-related difference in the level is less in comparison with women. Regarding these data, we hypothesised that high prevalence rate of pituitary incidentaloma in the elderly is associated with age-related decline in sex hormones levels and subsequent lack of feedback suppression leading to permanent gonadtrophs stimulation which is the crucial step in the pituitary tumour development. According to previously mentioned multistep model of pituitary tumourigenesis, incidentaloma will develop only in persons with already present intrinsic pituitary cell defects. However, further studies have to answer the questions of whether the incidence of pituitary tumours is more frequent in elderly, whether women with late onset menopause or those taking long-term hormone replacement therapy have lower rate of pituitary incidentaloma, and finally, is there any correlation between pituitary tumours incidence and serum concentrations of LH, FSH, bioavailable testosterone or estradiol.

Incidental pituitary adenoma is the common finding during brain imaging by computed tomography or magnetic resonance. In meta-analysis of a large number of autopsy studies the prevalence of pituitary incidentalomas is reported to be 11,3% (1). However, little is known about pathogenetic mechanisms of pituitary adenoma developing. Several animal models stress the role of hormonal stimulation in the pathogenesis of these tumours which is not in agreement with another theory favouring the intrinsic pituitary cell defects in the developing of pituitary adenoma. An integrated approach to these two concepts results in multistep model of pituitary tumourigenesis in which genetic alterations provide the initiating event that transforms cells while hormones play a role in promoting cell proliferation (2). The evidence for the important role of hormonal stimulation is the development of pituitary adenoma in a case of excessive hypophysiotrophic hormones production or reduced feedback suppression by target gland hormones. Pituitary hyperplasia has been reported in pregnancy (3), hypothyroidism (4) and conditions such as CRH or GHRH hypersecretion (5, 6).

Chanson et al. reported series of seven young women with incidentally discovered pituitary mass consistent with hyperplasia (7). Regarding the age of the patients, it could be related to gonadotroph cells involvement whose activity is supposed to be increased in peripubertal period. Recent study reported three cases of sellar mass in patients with Klinefelter syndrome, genetically determined disease characterised by primary gonadal defect (8). Gonadotroph macroadenoma has been found in one case and gonadtroph cells hyperplasia in other two. It tempts us to suggest that protracted stimulation of gonadotroph cells due to lack of androgen feedback might have been the most important factor in the formation of the pituitary masses in these patients. Conversely, in a small series of four patients with Turner syndrome no gonadotroph hyperplasia was present, but instead, corticotroph microadenomas were seen in three patients suggesting transdifferentiation of gonadotrophs to corticotrophs due to protracted stimulation of gonadotrophs or aberrant expression of gonadotropin-

releasing hormone (GnRH) receptors on corticotroph cells (9). In addition, antiandrogen administration in the male Sprague-Dawley rats produced a hypertrophia-hyperplasia of the follicle stimulating hormone (FSH) cells and hypertrophia of luteinizing hormone (LH) cells with marked alterations at the ultrastructural level suggestive of a hyperstimulation stage (10).

Significant changes of the hypothalamic-pituitary-gonadal axis occurred with aging in both, males and females. In females, after menopause, estradiol level decreases by 35-fold and estrone levels by 20-fold. The postmenopausal lack of estrogen results in increased gonadotropins levels and a decrease in the opioid inhibitory tone of GnRH secretion (11). In contrast to women, men do not experience a sharp decline in androgens level but rather slow decrease of gonadal function with age. However, only a minority of older men have elevated LH levels, while the majority have inappropriately normal LH due to pituitary defect (12). Conversely, FSH level is increased with advancing age in men, but the age-related difference in the level is less in comparison with women (13).

Regarding these data, we hypothesised that high prevalence rate of pituitary incidentaloma in the elderly is associated with age-related decline in sex hormones levels and subsequent lack of feedback suppression leading to permanent gonadotrophs stimulation which is the crucial step in the pituitary tumour development. It means that these incidentalomas are gonadotropinomas. According to previously mentioned multistep model of pituitary tumourigenesis, incidentaloma will develop only in persons with already present intrinsic pituitary cell defects. However, it would be expected to find a higher rate of pituitary tumours in women due to more abrupt rise of LH and FSH than in man. We believe that these tumours show a very little tendency for growth. Therefore, it could be of great interest to distinguish between these lesions from more aggressive pituitary tumours to avoid unnecessary frequent MRI surveillance and possible surgery.

Is developing of pituitary incidentaloma really associated with age-related decline of the sex hormones levels cannot be answered on the basis of so far published studies. Therefore further studies have to answer the questions of whether the incidence of pituitary tumours is more frequent in elderly, whether women with late onset menopause or those taking long-term hormone replacement therapy have lower rate of pituitary incidentaloma, and finally, is there any correlation between pituitary tumours incidence and serum concentrations of LH, FSH, bioavailable testosterone or estradiol.

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