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The influence of the tumoral cell proliferation rate in pituitary adenoma on expressing other factors with a prognostic role and therapeutic potential

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Abstract

Background: This article describes the growth rate of pituitary adenomas, their invasion and potential recurrence. Some of them grow rapidly while others remain in a dormant condition for a long time. The recurrence rate is also very hard to forecast. The pituitary adenomas that initially reduced their proliferation rate now acquire a rapid one, producing aggressive recurrences.
Materials and methods: Eighty two cases of pituitary adenomas were studied. The classification of human pituitary adenomas has been profoundly assisted by immunohistochemistry. Ki-67 antibody was used to assess the proliferative index of pituitary adenomas.
Results: Acidophil type adenomas or acidophil cells areas within mixed pituitary adenomas had the highest proliferation rate. Chromophobe pituitary adenomas were Ki67 negative in 90%, as well as the ones that presented the basophilic cells. The pituitary adenomas with a trabecular growth pattern had the lowest rate of proliferation, in about 50% of the cases being zero. The heterogeneity expression of growth factors and corresponding receptors is dependent on hormonal profile of pituitary adenomas.
Conclusion: The pituitary adenomas proliferation rate depends on the type of secreted hormone as well as on the hormonal associations met in some cases of pituitary adenomas.

Key words: pituitary adenoma, cell proliferation, Ki67.

Introduction

Pituitary adenomas are variable in growth rate, potential of invasion and recurrence. Some tumors grow fast; others remain in a dormant stage for a long time. The recurrence rate is also difficult to predict, the pituitary adenomas that initially reduced the proliferation rate acquire a fast proliferation rhythm and produce aggressive relapses. The ability to predict the proliferative potential of pituitary adenomas could have major implications for the clinical management of these tumors. Scientists have focused on identifying the predictive behaviour factors of pituitary adenomas. Ki67 proliferative index has been shown to be a useful tool in the measurement of tissue proliferation and for this reason, has been extensively studied.

Material and methods

Eighty two cases of pituitary adenomas were studied. The classification of human pituitary adenomas has been profoundly assisted by immunohistochemistry. Ki-67 antibody was used to assess the proliferative index of pituitary adenomas. Ki67 proliferation index was performed using Nikon Eclipse E600 microscope at 400X magnification assisted by a specialized cell counting computer program (NSI). The highest immunoreactivity areas were evaluated, an average of 1000 cells per case (about 3 microscopic fields taken as multimedia images) having been studied.

Results

Ki67 proliferation index in the pituitary adenomas was noted as being increased in cases with recurrences. There are no precise data on the pituitary hormones involvement in determining either the proliferation rate of pituitary adenomas or the growth factors. For this reason, the aim of the present study was to identify the potential role of pituitary hormones and growth factors, GFAP and S100 protein in influencing the pituitary adenomas proliferation rate. Proliferating pituitary adenomas represent 73.33% of all cases included in the study. Ki-67 expression was nuclear restricted the reaction intensity being variable, in most cases moderate and intense. The proliferation rate was extremely heterogeneous within this group, ranging between 4/1000 and 49/1000 (Fig. 1 a, b).

The highest proliferation rate was recorded in the acidophil type adenomas or acidophil cells areas within mixed pituitary adenomas. Pituitary adenomas of the chromophobe type were Ki67negative in 90%, like basophilc cell adenomas.

According to the growth pattern, papillary type pituitary adenomas were proliferative, the proliferation rate in most cases being greater than 20/1000.

Pituitary adenomas with trabecular growth pattern showed the lowest proliferation rate, in about 50% of cases it is zero. Pituitary adenomas with compact growth pattern had an average index of proliferation, being located between the papillary and the trabecular types. The proliferation index of compact pituitary adenomas is middle, being located between the papillary and trabecular types.

Afterwards, we analysed the pituitary adenoma proliferation rate in respect of their hormonal status. In 50% of plurihormonal pituitary adenomas there was no proliferation, the index being denoted by 0. The remaining plurihormonal type adenomas had a high proliferation index, 83.33% of which ranges between 21-41/1000.

Pure pituitary adenomas, which immunohistochemically expressed only one hormonal type were proliferating at a rate of 59% of the cases, 41% were not proliferative. Approximately 80% of GH-secreting pituitary adenomas were proliferating at a rate of proliferation medium ranges be-

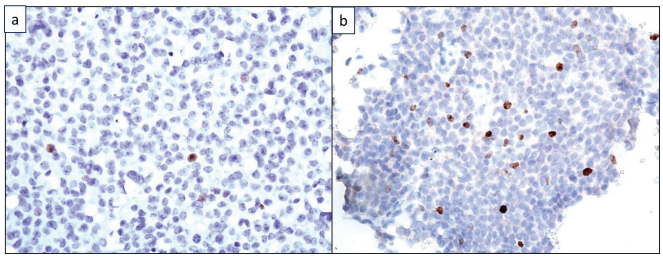

Fig. 1. Variability of proliferation of pituitary adenomas. Pituitary adenomas of low proliferation rate (a) and high proliferative rate (b).

tween 13-24 / 1000. About 80% of GH-secreting pituitary adenomas were proliferating at a medium proliferation rate that ranges between 13-24/1000.

The co-expression of LH – FSH denotes tumor cells proliferation. All LH -FSH positive cases were proliferating, but at a relatively low proliferation rate, in 60% of cases within the limits of 6-12 / 1000.

Non-secreting pituitary adenomas were proliferating in an amount of 77.8%. 57.14% of the proliferating cases had an average rate of proliferation, between 11-20 / 1000. In this study we identified other hormonal combinations, different from those specified before. Their number was reduced so that these particular types required a separate analysis. Thus, the PRL -ACTH hormonal combination was found in one case of papillary adenoma predominantly basophilic with acidophilic areas where the proliferation rate was very high, i.e. 30/1000. Another isolated case of GH-TSH hormone profile also presented a relatively high rate of proliferation of 20/1000. However, in most hormonal profile associations in which one of the hormones had been LH, the tumor cell proliferation rate was 0. In fact, it was the only hormone for which we obtained a statistically significant inverse correlation with Ki67 proliferation index taken from the Table correlation shown in figure 2.

Discussion

In 2004, the World Health Organization included a new subtype – "atypical" adenoma in the classification of pituitary adenomas. This entity has the following characteristics: a tumor proliferation index (Ki67) greater than 3%, p53 over expression and increased mitotic rate [1]. This new variant of adenoma is actually an intermediate step between conventional adenomas and pituitary carcinoma (tumor entity that represents less than 1% of primary pituitary tumors) [2]. In most published studies, the proliferative index Ki-67 is linked to the hormonal profile of adenomas, the size and the degree of invasion thereof as determined by high-resolution imaging. There is no correlation between Ki67 and architectural pattern of adenomas or its tinctorial character at the cytoplasmic level.

In his study Pawlikowski et al. [3] demonstrated that polyhormonal pituitary adenomas show higher Ki67values than the monohormonal ones, in particular those which co-express ACTH. In a previous study, the same researcher evaluated another proliferation nuclear marker – PCNA and the same results were found [4]. The lowest values of proliferation markers were recorded for non-secreting adenomas in both previous studies. Our study has shown similar results; the proliferation marker is highest in polyhormonal adenomas and lower in the case of non-secreting adenomas. On the other hand, there are studies that have shown other types of adenomas to have a higher proliferative index, such

		Ki 67	LH
Ki67	Pearson Correlation	1.000	-.247
	Sig. (1-tailed)	.	.027
	N	61	61
LH	Pearson Correlation	-.247	1.000
	Sig. (1-tailed)	.027	.
	N	61	61

			Ki 67	LH
Kendall's tau_b	Ki 67	Correlation Coefficient	1.000	-.206
		Sig. (1-tailed)	.	.023
		N	61	61
	LH	Correlation Coefficient	-.206	1.000
		Sig. (1-tailed)	.023	.
		N	61	61
Spearman's rho	Ki 67	Correlation Coefficient	1.000	-.265
		Sig. (1-tailed)	.	.020
		N	61	61
	LH	Correlation Coefficient	-.265	1.000
		Sig. (1-tailed)	.020	.
		N	61	61

Fig. 2. The statistical analysis of correlation between Ki67 proliferation index and LH is shown. An inverse correlation between the expression of LH and proliferation rate is noted.

as prolactinoma [5] or ACTH-secreting adenomas [2, 6]. Some studies suggest that prolactinoma with increased proliferation index, besides the risk of recurrence, is pituitary carcinomas precursors [6].

The data given in literature indicate low levels of proliferation marker Ki 67 in both gonadotropic hormone-secreting adenomas, and non-secreting ones [1, 6, 7].

In addition to existing data, the present study has demonstrated that polyhormonal adenomas including co-expression of LH present a low proliferation index.

Conclusions

1. The heterogeneity expression of growth factors and corresponding receptors is dependent on hormonal profile of pituitary adenomas.

2. Secreting GH and PRL pituitary adenomas are the most active in terms of synthesis and release of growth factors.

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