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BRIEF ORIGINAL

Prognostic implications of telomerase expression in pituitary adenomas☆

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KEYWORDS
Pituitary adenoma;
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Abstract
Objectives: To analyze the prognostic value of telomerase expression in patients with pituitary adenomas (PAs) followed-up for at least 8 years.
Patients and methods: A retrospective study was conducted of samples from 51 PAs (40 typical and 11 atypical) from patients who underwent transsphenoidal surgery between 2006 and 2008 and from 10 normal pituitary glands obtained by autopsy. Telomerase expression was assessed by immunohistochemistry, correlating the expression with that of Ki-67 and p53.
Results: We observed telomerase expression in 43 PAs (84.3%, 32 of the 40 typical PAs and in the 11 atypical PAs), which was higher in the clinically nonfunctioning cases ($p = 0.0034$) and very rare in the patients with acromegaly ($p = 0.0001$). There was a significant association between the percentage of tumor cells (>10%) and the recurrence of the adenoma ($p = 0.039$). There was no correlation with the expression of Ki-67 and p53 ($p = 0.4986$), and there were no differences according to age, sex, tumor size and invasiveness.
Conclusions: A telomerase expression rate greater than 10% in the pituitary tumor tissue was associated with recurrence or progression of the PA, especially in the nonfunctioning cases.

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PALABRAS CLAVE
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transcriptasa inversa

Implicación pronóstica de la expresión de telomerasa en adenomas hipofisarios

Resumen
Objetivos: Analizar el valor pronóstico de la expresión de telomerasa en pacientes con adenomas hipofisarios (AH) seguidos durante al menos 8 años.
Pacientes y métodos: Estudio retrospectivo de las muestras de 51 AH (40 típicos y 11 atípicos) de pacientes sometidos a cirugía transesfenoidal entre 2006 y 2008, y de 10 hipófisis normales obtenidas por autopsia. Se evaluó la expresión de telomerasa por inmunohistoquímica correlacionándola con la de Ki-67 y p53.
Resultados: Se observó expresión de telomerasa en 43 AH (84,3%, 32 de los 40 típicos y en los 11 atípicos), siendo mayor en los casos clínicamente no funcionantes (p = 0,0034) y muy escasa en los pacientes con acromegalia (p = 0,0001). Hubo una asociación significativa entre el porcentaje de células tumorales (>10%) y la recurrencia del adenoma (p = 0,039). No hubo correlación con la expresión de Ki-67 y p53 (p = 0,4986) ni se observaron diferencias en función de la edad, el sexo, el tamaño o la invasividad tumoral.
Conclusiones: Un índice de expresión de telomerasa mayor del 10% en el tejido hipofisario tumoral se asoció a recurrencia o progresión del AH, especialmente en los no funcionantes.

Background

Pituitary gland and sellar region tumors represent approximately 15% of brain tumors,[1] with pituitary adenomas (PAs) the most common neoplasms.[2] Although most PAs are benign,[3] there is a subgroup whose presentation and biological activity are borderline between benignity and malignancy. Despite progress in understanding the pathogenesis of PAs, no marker has been identified to independently predict their aggressive behavior.

Telomeres are a specialized structure located at the end of the eukaryotic chromosome whose function is to prevent normal cells from reproducing indefinitely.[4] The persistence of telomeres is attributable to the telomerase, a ribonucleoprotein enzyme charged with maintaining homeostasis and chromosomal integrity. Telomerase is composed of 3 subunits: human telomerase reverse transcriptase, human telomerase ribonucleic acid and telomerase-associated protein 1. An imbalance between telomeres and this enzyme (or its activation) is a critical step in the development of cancer.[5]

Telomerase's activity level is unquantifiable in most normal cells[6] but is expressed in immortalized cells, such as tumor cells.[7] The degree of expression is directly correlated with the prognosis in certain tumors.[8–10]

The aim of this study was to analyze the prognostic utility of the immunohistochemical expression of telomerase in samples of pituitary tumor tissue from patients with PA, followed for at least 8 years.

Patients and methods

A descriptive, retrospective study was conducted of samples from 51 PAs from 26 women and 25 men with a mean age of 54.5 ± 14.5 years and a clinical follow-up of at least 8 years. The PA diagnosis was based on the clinical/biological condition and on the histopathological examination, according to the WHO criteria.[11] Thirty-three tumors were nonfunctional (NF), 13 produced growth hormones, 4 produced adrenocorticotropic hormones and 1 produced prolactin.

The histopathology studies were performed with tissue sections that were stained with histochemical (hematoxylin–eosin and reticulin) and immunohistochemical techniques (with specific primary antibodies against all anterior pituitary hormones, with a marker of cell proliferation [Ki-67] and with a marker of the tumor suppressor gene p53). Telomerase expression was studied using automated immunohistochemistry (Ventana BenchMark XT, US) using polyclonal antibodies (origin, Abcam; dilution, 1/100). The number of stained tumor cells was calculated semiquantitatively by the same pathologist, and the result was classified as negative or positive (with 3 variants: <10%, 10–50% and >50% of the cells in 500–1000 tumor cells) (Fig. 1). In equivocal cases, the percentage was calculated with an image processing program for immunohistochemical analysis (Image J 1.49, National Institutes of Health, US).

As a control group, samples of 10 normal pituitary glands were examined, which were obtained from autopsies of patients between 26 and 83 years of age (mean age, 67.8 ± 12.9 years). Telomerase expression was correlated with tumor progression or recurrence.

We performed basic comparative and statistical analyses for the data distributions, using a 2-tailed Fisher's exact test to compare the categorical data and an unpaired Student's *t*-test to compare the subgroups with the telomerase expression. Statistical significance was defined as a *p*-value <0.05.

Results

Of the total of 51 PAs, 40 were classified as typical and 11 as atypical. Telomerase expression was positive in 43 cases (84.3%), of which 17 (33.3%) showed tumor cell staining of