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ORIGINAL ARTICLE

Pituitary tumor transforming gene and insulin-like growth factor 1 receptor expression and immunohistochemical measurement of Ki-67 as potential prognostic markers of pituitary tumors aggressiveness

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KEYWORDS
Pituitary adenoma;
Pituitary tumor transforming gene protein;
Humans;
Ki-67 antigen;
Insulin-like growth factor 1 receptor

Abstract
Introduction and objective: The ability to predict recurrence of pituitary adenoma (PA) after surgery may be helpful to determine follow-up frequency and the need for adjuvant treatment. The purpose of this study was to assess the prognostic capacity of pituitary tumor transforming gene (PTTG), insulin-like growth factor 1 receptor (IGF1R), and Ki-67.
Materials and methods: In this retrospective study, the normalized copy number (NCN) of PTIG and IGF1R mRNA was measured using RT-PCR, and the Ki-67 index was measured by immunohistochemistry in 46 PA samples. Clinical data, histological subtype, and radiographic characteristics were collected to assess associations between variables and tumor behavior. Progression of tumor remnants and its association to markers was also studied in 14 patients with no adjuvant treatment after surgery followed up for 46 ± 36 months.

Abbreviations: PA, pituitary adenomas; PTTG, pituitary tumor transforming gene; IGF1R, insulin-like growth factor 1 receptor; RT-PCR, real time polymerase chain reaction; PI3K/Akt, phosphoinositide 3-kinase/Akt pathway; MAPK, mitogen-activated protein kinases; MRI, magnetic resonance imaging; FFPE, formalin-fixes and paraffin-embedded; FPA, functioning pituitary adenoma; NFPA, non-functioning pituitary adenoma; PRL, prolactin; ACTH, adrenocorticotropic hormone; GH, growth hormone; TSH, Thyroid stimulating hormone; DA, dopamine agonist; SSa, somatostatin analogs; ROC, receiver operating characteristics; LT, lactotrophic adenomas; CT, corticotrophic adenomas; TT, Thyrotrophic adenomas; ST, somatotrophic adenomas; GT, gonadotrophic adenomas; NC, null-cell adenomas.

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Results: Extrasellar tumors had a lower PTTG expression as compared to sellar tumors (0.065 [1st–3rd quartile: 0.000–0.089] NCN vs. 0.135 [0.105–0.159] NCN, $p = 0.04$). IGF1R expression changed depending on histological subtype ($p = 0.014$), and was greater in tumor with remnant growth greater than 20% during follow-up (10.69 ± 3.84 NCN vs. 5.44 ± 3.55 NCN, $p = 0.014$).
Conclusions: Our results suggest that the IGF1R is a more helpful molecular marker than PTTG in PA management. Ki-67 showed no association to tumor behavior. However, the potential of these markers should be established in future studies with standardized methods and on larger samples.

PALABRAS CLAVE
Adenoma hipofisario;
Proteína del gen transformador de tumores hipofisarios;
Humanos;
Antígeno Ki-67;
Receptor del factor de crecimiento insulinoide 1

Expresión del gen transformador de tumores hipofisarios y del receptor del factor de crecimiento insulinoide 1 y determinación inmunohistoquímica de Ki-67 como posibles marcadores pronósticos de la agresividad de los tumores hipofisarios

Resumen
Introducción y objetivo: La capacidad de predecir recurrencia en los adenomas hipofisarios (AH) tras la cirugía puede ser útil para determinar la frecuencia de seguimiento y la necesidad de tratamientos adyuvantes. El objetivo del presente estudio fue valorar la capacidad pronóstica de gen transformador de tumores hipofisarios (*pituitary tumor transforming gene* [PTTG]), del receptor del factor de crecimiento insulinoide 1 (*insulin-like growth factor 1 receptor* [IGF1R]) y de Ki-67.
Material y métodos: En este estudio retrospectivo determinamos el número de copias normalizadas de ARNm (Cnn) de PTTG e IGF1R mediante RT-PCR y el índice Ki-67 mediante inmunohistoquímica en 46 muestras de AH. Los datos clínicos, el subtipo histológico y las características radiológicas se recogieron para determinar asociaciones entre las variables y el comportamiento tumoral. Además, estudiamos la progresión de los restos tumorales y su asociación con los marcadores en 14 pacientes sin tratamiento adyuvante posquirúrgico seguidos durante 46 ± 36 meses.
Resultados: Los tumores extraselares mostraron una expresión de PTTG menor que los intraselares (0,065 [1.er-3.er cuartil: 0,000-0,089] Cnn frente a 0,135 [0,105–0,159] Cnn, p = 0,04). La expresión de IGF1R varió en función del subtipo histológico (p = 0,014), siendo mayor en los tumores que presentaron crecimiento de los restos mayor del 20% durante el seguimiento ($10,69 \pm 3,84$ Cnn frente a $5,44 \pm 3,55$ Cnn, p = 0,014).
Conclusiones: Nuestros resultados indican que IGF1R, en mayor medida que PTTG, es un marcador molecular útil en el manejo de los AH. Ki-67 no mostró asociación con el comportamiento tumoral. Sin embargo, el potencial de estos marcadores debe ser establecido en futuros estudios con una metodología estandarizada y una muestra mayor.

Introduction

Pituitary adenomas (PA) constitute 10–25% of intracranial neoplasms. They are almost always benign, but some show aggressive behavior with local invasion and recurrences. Several sporadic mutations of oncogenes and tumor-suppressor genes have been found in PA, but none has been found to be a reliable marker of poor outcome.[1,2] In clinical practice, Ki-67 antigen expression is frequently used as a prognostic indicator because it has been associated with proliferative potential and invasiveness of several human malignancies, but it has shown discordant results in pituitary adenomas.[3,4]

Thus, there is an increasing interest in finding specific prognostic markers. Pituitary tumor transforming gene (PTTG) encodes a protein that functions like securin and transcription factor.[5,6] It is involved in the cell cycle regulation and may induce cellular proliferation and aneuploidy.[6,7] Overexpression of PTTG has been described in several neoplasms including PA.[8–10]

IGF1R is a tyrosine kinase receptor responsible for mediating IGF-I signaling, which plays a critical role in normal growth and has been associated with the early stages of tumor establishment. IGF1R stimulates the PI3K/Akt and MAPK pathways,[11] resulting in cell proliferation and apoptosis alteration. Its overexpression has been documented in many human malignancies[12] but it is not yet well studied in PA.

The aim of this study is to examine whether PTTG and IGF1R expression or Ki-67 index may have prognostic implications on pituitary adenomas.

Materials and methods

Subjects

This is a retrospective study performed at Hospital General Universitario de Alicante including patients who underwent