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Original article

Alpha subunit in clinically non-functioning pituitary adenomas: An immunohistochemical study

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ABSTRACT

Pituitary adenomas may be classified as either functioning or non-functioning, depending on whether excess hormone secretion can be clinically identified. Of the six hormones produced in the anterior pituitary, TSH, FSH and LH are known as glycoproteins and contain two subunits (α and β). While α-subunit is identical within all of them, each β-subunit is unique and biologically specific. Independently, the α- and β-subunits are inactive and only induce a hormonal response when they are non-covalently associated. Studies have shown that in certain cases, pituitary adenomas may abnormally secrete only α-subunit, detectable in the serum or through immunohistochemical analysis. In the present study, we examined α-subunit immunoexpression in surgically removed non-functioning pituitary adenomas and analyzed its prognostic value. Results showed that expression of α-subunit in clinically non-functioning pituitary adenomas is not a rare occurrence. While there were no age/gender differences between tumors that expressed α-subunit and those that did not, α-subunit immunonegative adenomas presented with suprasellar extension more frequently and had an Ki67 proliferation greater than 3%. The use of immunohistochemical techniques to determine the presence of α-subunit may provide information on tumor cell proliferation and biologic behavior. To fully understand the role of α-subunit in pituitary adenomas more work is needed.

1. Introduction

Pituitary adenomas (PA) are benign, intra-sellar neoplasms arising in adenohypophysial cells, which account for nearly 15% of all intracranial tumors [1]. While typically benign, PAs may extend beyond the sella and invade areas such as the cavernous sinus and suprasellar cistern, producing mass effects on surrounding structures, such as the optic chiasm [2,3]. Pituitary adenomas may be either functional or non-functional. Functional PAs produce excess amounts of prolactin (PRL), growth hormone (GH), adrenocorticotropic hormone (ACTH) or thyroid-stimulating hormone (TSH), resulting in characteristic physiological sequelae for the individual (Fig. 1). Non-functional pituitary adenomas (NFPA) generally produce follicle-stimulating hormone (FSH), luteinizing hormone (LH) and/or α-subunit. Although they are not physiologically active, immunohistochemical analysis of the tumor reveals, in fact, their production (Fig. 2). NFPAs usually go unnoticed until they have grown to a sufficient size to compress the optic chiasm or cause hypopituitarism. Patients may also report worsening headaches and fatigue. While surgical resection remains the most effective treatment for these lesions, more aggressive adenomas may recur, often requiring repeated surgeries, radiation, and/or chemotherapy [4,5]. Currently, there is no gold standard to predict the likelihood of adenoma recurrence, but some techniques, including the Ki-67/MIB-1 labeling index, may have some prognostic value [6]. Given their functional diversity and behavior, much attention has been placed on correlative clinicopathological studies.

Of the six hormones produced by the anterior pituitary, TSH, FSH and LH are glycoprotein heterodimers consisting of two α- and two β-subunits [7]. The α-subunit is the same in all of them, while each β-subunit is unique and imparts biological specificity. Alone, the α- and β-subunits are inactive and only induce a hormonal response when they are non-covalently associated. In some cases, a PA may abnormally secrete the α-subunit independently

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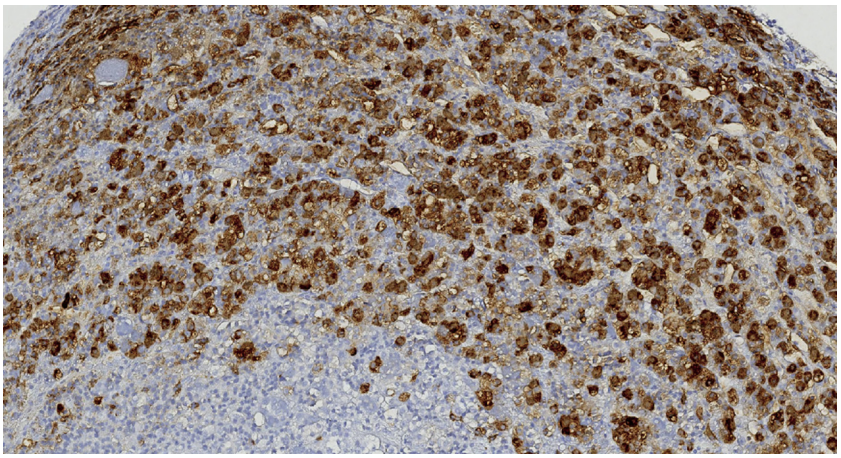

Fig. 1. Many pituitary adenoma cells showing cytoplasmic immunopositivity for α-subunit. Original magnification: 200×.

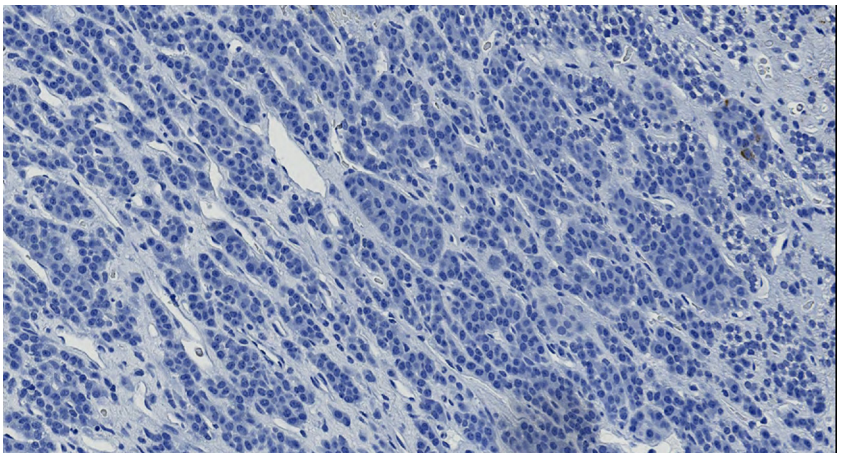

Fig. 2. Immunostaining showing the cells in this pituitary adenoma are negative for α-subunit despite the fact that there was mild focal immunopositivity for LH in the cytoplasm of several cells. Original magnification: 200×.

from the β-subunit. This free α-subunit is often detectable in the patient's serum or through immunohistochemical analysis of the tumor [8,9].

To date, the clinical relevance of the glycoprotein α-subunit has not been evaluated extensively. In the current study, we examined α-subunit immunoexpression in surgically removed NFPA and analyzed its prognostic value. The series of PAs studied represents one of the largest study groups that has been analyzed using endocrine, immunohistochemical (IHC), radiologic and surgical data.

2. Material and methods

Data was collected from patients who underwent surgery for resection of NFPAs via a transsphenoidal or craniotomy approach at St. Michael's Hospital (Toronto, Ontario, Canada) between 1998 and 2014, using the hospital information system (Soarian Clinicals). Case selection focused strictly on NFPAs and 277 patients with complete clinical data were eligible for inclusion into the study (171 male, 106 female). Demographic information including gender and age at surgery was collected, in addition to clinical data, which included symptoms, tumor size, surgical outcome and recurrences. Recurrences were identified if regrowth of the tumor was evident on radiological follow-up and repeated surgical resection was needed. PRL, GH, ACTH and TSH blood levels were within normal ranges before surgery and patients did not show any signs of acromegaly, gigantism, Cushing's disease or hyperthyroidism. Tumor volume was calculated using the formula $V = \left(\frac{4}{3}\right) \times \pi \times \left(\frac{L}{2}\right) \times \left(\frac{W}{2}\right) \times \left(\frac{D}{2}\right)$, where L is the tumor length, W is the tumor width, and D is the tumor depth as measured on preoperative magnetic resonance imaging (MRI) scans [10]. Specimens were formalin-fixed, dehydrated in graded ethanol, and paraffin-embedded. Immunohistochemical analysis was performed using antisera directed towards the anterior pituitary hormones and the α-subunit of the glycoprotein hormones. Final classification was based on the criteria defined by the World Health Organization [11]. The cases were divided into two groups, depending on the presence or absence of the α-subunit at immunohistochemistry. Group 1, comprised of patients negative for α-subunit and Group 2 comprised of patients positive for α-subunit alone, or with another anterior pituitary hormone. For statistical analysis, two-tailed Fisher's exact test were employed. This study was performed with approval from the Research Ethics Board at St. Michael's Hospital.

3. Results

From the 277 patients included in the study (Table 1), Group 1 consisted of 147 patients negative for α-subunit (89 male, 58 females; age range: 25–90; mean age: 55.5). Group 2 consisted of 130 patients positive for α-subunit (82 male, 48 females; age range: 20–83; mean age: 58.0), with five of these patients being positive for α-subunit alone. The α-subunit negative group was larger in

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