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Hypopituitarism patterns among adult males with prolactinomas

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ABSTRACT

Objectives: The objective of this study was to characterize hypopituitarism in adult males with prolactinomas.
Patients and methods: We retrospectively analyzed the records of 102 consecutive patients, classified under three categories based on adenoma size at diagnosis: 1.0–2.0 cm (group A), 2.1–4.0 cm (group B), and >4.0 cm (group C). Further, 76 patients had successful outcomes at follow-up. We compared different forms of pituitary hormone dysfunction (growth hormone deficiency, hypogonadism, hypothyroidism, and hypocortisolism) based on the maximal adenoma diameter.
Results: Serum prolactin levels were significantly correlated with the maximal adenoma diameter ($r = 0.867$; $P = 0.000$). Of the patients, 89.2% presented with pituitary failure, which included 74.5% with growth hormone deficiency, 71.6% with hypogonadism, 28.4% with hypothyroidism, and 12.7% with hypocortisolism. The three groups did not differ significantly ($P > 0.05$) in the incidence of hypopituitarism, including the extent of pituitary axis deficiency, at presentation and following treatment. However, there was a statistically significant difference in the degree of hypogonadism in cases of acquired pituitary insufficiency at diagnosis ($P = 0.000$).
Conclusion: In adult males with prolactin-secreting adenomas, the most common form of pituitary hormone dysfunction was growth hormone deficiency and hypogonadism, whereas hypocortisolism was less common. The maximal adenoma diameter and prolactin secretion did not determine hormone insufficiency in adult males with prolactinomas, but these factors did affect the degree of both hypogonadism and hypothyroidism. Smaller tumors were found to recur more frequently than large tumors, and recovery was more common in cases of growth hormone deficiency and hypogonadism.

1. Introduction

Prolactinomas are the most common type of benign hormone-secreting pituitary tumors. Annually, approximately 30 cases per million people [1] are reported, which account for approximately 60% of primary pituitary adenomas.

The prevalence of pituitary tumors would be much higher if clinically insignificant microadenomas were also included; these microadenomas are discovered in approximately 11% of pituitaries at autopsy, 46% of which immunostain positively for prolactin (PRL) [2]. Prolactinomas are more common in women than in men. Interestingly, the tumor size typically differs between genders at presentation or diagnosis, with women developing microprolactinomas (<10 mm) and men macroprolactinomas (>10 mm) [3], at ratios of 20:1 and 1:1, respectively [4]. The clinical symptoms of prolactinomas usually develop due to hyperprolactinemia with or without hypopituitarism, as well as from the tumor mass effect. While women tend to present with symptoms of amenorrhea/galactorrhea due to hyperprolactinemia, men may present with decreased libido and impotence, and/or symptoms secondary to mass pressure such as headaches or visual field defects.

The goals of prolactinoma treatment are to normalize serum PRL levels, remove the tumor or decrease tumor size, and promote recovery from hypopituitarism. Previous studies revealed the extremely high mortality rate among patients with hypopituitarism, predominantly due to vascular and respiratory disease [5]. Furthermore, the positive correlation between adenoma size and hypopituitarism has already been reported in patients with non-functioning pituitary adenomas (NFPAs) [6]. It can be concluded that hypopituitarism is more prevalent among adult males with

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prolactinomas than among female patients. Thus, further information on their clinical and laboratory characteristics is necessary to address hormone insufficiency.

In this large cohort of male patients with prolactinomas, we aimed to evaluate the correlation between adenoma size and hypopituitarism patterns at diagnosis. We also investigated the recovery of pituitary hormone function following treatment with dopamine agonists (DAs) and surgery.

2. Patients and methods

The study included 102 adult males with prolactinomas, defined as those with plasma PRL levels five times the upper limit of normal values (ULN) and with an obvious sellar region mass [7]. All of these patients were diagnosed, treated, and followed up in the Department of Neurosurgery at Nanfang Hospital, Guangdong, China, between 2008 and 2013. The results of the laboratory tests (PRL, total testosterone (TESTO), luteinizing hormone (LH), follicle-stimulating hormone (FSH), cortisol (COR), thyroid function tests, growth hormone (GH), and insulin-like growth factor-1 (IGF-1)), pituitary imaging findings, and tumor size measurements were noted for every patient. The maximal adenoma diameter, reflecting tumor size, was calculated based on the computed tomography (CT) or magnetic resonance imaging (MRI) scans. All patients were categorized based on the maximal adenoma diameter at presentation: 1.0–2.0 cm (group A), 2.1–4.0 cm (group B), and >4.0 cm (group C). The visual field damage in these patients was assessed by the Department of Ophthalmology at Nanfang Hospital, using equipment for measuring vision and field. However, the visual impairment was only reported to be a small deficit or a blindness in this study.

Minors, patients treated in other hospitals, and those with indefinite diagnosis were excluded from this study.

2.1. Endocrinological assessment

The hormonal levels were determined at baseline in the laboratory of our hospital using standard radioimmunoassay kits according to the manufacturer's instructions. Hypopituitarism was defined as partial or complete loss of the hypothalamic–pituitary axis [8]. Growth hormone deficiency (GHD) was diagnosed based on low serum levels of IGF-1 or on the results of the insulin tolerance test (ITT) [9]. Gonadotrophin deficiency was defined as low or abnormal FSH and LH levels as well as low TESTO levels [10]. Central hypothyroidism was defined as low or abnormal TSH levels in the presence of low levels of free T4 (FT4) [11]. Central hypocortisolism was defined as serum cortisol levels <3 μg/dL at 09:00 a.m. or peak cortisol levels <20 μg/dL after ITT [12].

2.2. Follow-up

In general, patients were followed up several times in the first year after treatment and thereafter at 6–12-month intervals based on the attending physician's discretion as well as the laboratory workup and imaging findings for the same time intervals. As in our routine practice, patients undergo MRI scanning 3 months after therapy primarily for evaluating the chiasmal pressure and sellar anatomy, and 1 year post treatment, at which time the remaining measurements are performed as baselines for future imaging studies. The primary outcomes included the rate of recovery from hypopituitarism and visual field impairment following initial therapy. The secondary outcomes included the need for disease-related mortality and the overall mortality.

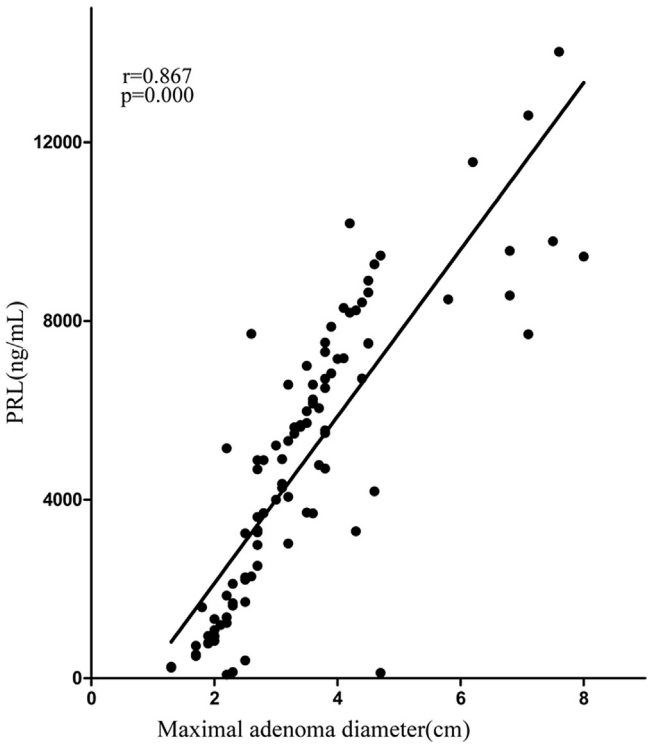

Fig. 1. A correlation between serum PRL level and tumor size.

2.3. Statistical analysis

Statistical calculations were performed with the SPSS 19.0 statistical analysis software (SPSS Inc., Chicago, IL, USA). Continuous data are presented as means and standard deviations or medians and ranges, as needed for each variable. For between-group comparison, the independent Student's *t*-test or one-way analysis of variance (ANOVA) was conducted to analyze the differences among the numerical variables, and the chi-squared test was used to determine the differences among the categorical variables. The Pearson product was used to analyze the correlations among variables. The observed differences were assumed to be statistically significant at a p-value <0.05.

3. Results

3.1. Baseline characteristics

The study cohort included 102 men with a mean age of 39.70 ± 11.85 years at diagnosis. The mean adenoma size was 3.44 ± 1.41 cm. The mean PRL level was 4812.5 ± 3151.5 ng/mL. Of the 102 patients, 59 (57.8%) presented with significant visual damage and 56 (54.9%) with decreased libido and impotence. Fourteen patients were found to have adenomas in group A, 63 in group B, and 25 in group C. The clinical and laboratory characteristics of the patients included in the study are shown in Table 1, based on the maximal adenoma diameter at presentation. No significant differences were found among the three groups ($P > 0.05$) in terms of age, FT4 levels, and 9:00 a.m. COR levels at initial diagnosis. Significant differences were also noted in visual field damage, sexual dysfunction, and PRL and TESTO levels ($P < 0.05$). The PRL level and maximal tumor diameter were found to be positively correlated ($r = 0.867$; $P = 0.000$) in this series (Fig. 1).

At initial diagnosis, hypopituitarism was found in 89.2% (91/102) of patients, followed by GHD, hypogonadism, hypothyroidism, and hypocortisolism in 74.5%, 71.6%, 28.4%, and 12.7%,