**CLINICAL SIGNIFICANCE OF ANEMIA ASSOCIATED WITH
PROLACTIN-SECRETING PITUITARY TUMORS IN MEN**

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**CLINICAL SIGNIFICANCE OF ANEMIA ASSOCIATED WITH
PROLACTIN-SECRETING PITUITARY TUMORS IN MEN**

(Revised version-R1)

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Abstract

BACKGROUND An association between prolactin-secreting pituitary adenomas and anemia in male patients has been recently reported. Our aim has been to evaluate the prevalence of anemia in men with prolactinomas and to assess the relationships between hemoglobin concentrations and pituitary function at diagnosis in these patients.

METHODS In a retrospective analysis 26 male patients with prolactinomas (22 macroprolactinomas and 4 microprolactinomas) were studied. Blood hemoglobin concentration, hematocrit value and baseline hormonal levels were collected at the time of prolactinoma diagnosis. The presence or absence of partial or total hypopituitarism was also evaluated at diagnosis. Logistic regression analysis was used to assess the presence of anemia as a function of serum hormone concentrations and pituitary dysfunction.

RESULTS Patient bearing macroprolactinomas showed significant lower hemoglobin concentrations than those found in patients with microprolactinomas (13.5 ± 1.2 g/dl vs. 15.1 ± 0.9 g/dl, $p < 0.05$). Anemia (hemoglobin < 13 g/dl) was present in 9 (34.6%) patients, all of them with macroprolactinomas. The degree of anemia was mild (hemoglobin > 11 g/dl) in all patients. No correlation between hemoglobin and serum prolactin was found. Hemoglobin concentration was significantly lower in men with hypogonadism ($n=14$) than in eugonadal men. Hemoglobin value was also significantly lower in patients with total hypopituitarism in comparison with subjects with partial hypopituitarism (12.4 ± 1.0 g/dl, $n=7$ vs. 14.0 ± 1.2 g/dl, $n=13$ $p=0.007$). The number of affected pituitary axes was found to be related with the presence of anemia. Logistic regression analysis showed that anemia was related with FT4 (OR 0.23; 95% C.I. 0.06-0.81, $p=0.02$), cortisol (OR 0.81; 95% C.I. 0.68-0.96, $p=0.02$) and the presence of hypopituitarism (OR 20.0; 95% C.I. 1.68-238.63, $p=0.02$).

CONCLUSIONS Anemia was found in about a third of men with prolactinomas. Our results also suggest that the presence of anemia in these patients seems to be associated with panhypopituitarism.

What's known

- An association between anemia and macroprolactinomas in male patients has been documented.
- Anemia has been related with hypogonadism and tumor size in these patients.

What's new

- Mild normocytic and normochromic anemia is found in about a third of men with prolactinomas.
- The presence of anemia in these patients seems to be associated with macroprolactinoma induced panhypopituitarism.

Introduction

Prolactinomas are the most common hormone-secreting pituitary tumors, accounting for about 60% of primary pituitary tumors. These tumors are more frequently seen in women (>70%) than in men (1-3). The female/male ratio varies depending on the tumor size, being 20:1 and 1:1 for micro- (≤ 10 mm) and macroprolactinomas (>10 mm), respectively (4).

It has been reported that hematopoiesis is compromised in men who have low concentrations of testosterone due to a pituitary adenoma, supporting a direct relationship between serum testosterone levels and hematopoiesis in men (5). More recently, an association between anemia and macroprolactinomas in male patients has also been documented (6). In this setting, anemia was related with hypogonadism and tumor size and an improvement in hemoglobin concentrations have been reported after achieving normalization of PRL levels and increase in testosterone concentrations with appropriate therapy (6).

To our knowledge the relationship between pituitary function and the presence of anemia has not been extensively evaluated in male patients bearing prolactinoma. Our aim was to assess the prevalence of anemia associated with prolactinoma and to analyze its relationship with pituitary function at diagnosis in male patients with prolactin-secreting pituitary adenomas.

Patients and methods

Patients

We retrospectively investigated the presence of anemia at diagnosis of PRL-secreting pituitary tumors in 26 men and followed-up in the last 35 years at 2 centers: Hospital Ramón y Cajal (Madrid, Spain) and hospital General (Segovia, Spain). The diagnosis of prolactinoma

was made either immunohistologically after surgery or meeting the following clinical diagnostic criteria: a mean serum PRL level ≥ 35 ng/ml associated with pituitary tumor (≤ 10 mm) in the computed tomography (CT) or magnetic resonance imaging (MRI) for microprolactinomas and a mean serum PRL level ≥ 200 ng/ml and a pituitary tumor (>10 mm) in CT or MRI study for macroprolactinomas. None of the patients took drugs known to modify PRL concentrations at the moment of the study.

Analytical variables

In every patient we assessed the following analytical data at the time of prolactinoma diagnosis: hemoglobin (Hb) concentration, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), white blood cell (WBC), platelet counts and baseline hormonal levels of concentrations [thyrotropin, TSH (N: 0.350-4.950 mU/l); free thyroxine, FT4 (N: 0.70-1.48 ng/dl); follicle stimulating hormone, FSH (N: 3.5-12.5 mU/ml); luteinizing hormone, LH (N: 2.4-12.6 mU/ml); testosterone (N: 300-900 ng/dl); cortisol (N: 5-25 mcg/dl); and insulin-like growth factor type 1, IGF 1 (N: 109-284 ng/ml)]. Anemia was defined by using the World Health Organization criteria (Hb level <13 g/dl in men) (7). We also assessed the presence or absence of hypopituitarism at diagnosis registering type and number of pituitary deficiencies. Central hypogonadism was defined when serum testosterone was lower than 300 ng/dl and low or low-normal gonadotropin levels (8). Hb, hematocrit, and hormone measurements were performed in the laboratories of each hospital using standard automated blood count analyzer, radioimmunoassay, immunoradiometric assay or enzymeimmunoassay methods.

Statistical analysis

For quantitative variables, results are expressed as mean $\pm$ SD for normally distributed data, and as median (interquartile range) for nonparametric data. Adjustment to normal distribution was tested by the Kolmogorov test. Categorical variables are described as percentages. For comparisons of means between two groups of subjects the Student t-test was used for normally distributed data, and the Mann-Whitney test was employed for nonparametric data. For ratio comparisons the chi-square test was used. Correlations between quantitative variables were assessed using Pearson's correlation analysis. Models of logistic regression analysis were used to assess the presence of anemia at diagnosis of prolactinomas as a function of several qualitative and quantitative variables (serum hormone concentrations). Differences were considered significant when $p < 0.05$.

Results

Clinical features and analytical data

A group of 26 men (age 38.8 ± 15.4 years) with prolactinomas was evaluated. Twelve prolactinomas (46.2%) were diagnosed immunohistologically. The rest of the patients (n=14, 53.8%) met all the clinical diagnostic criteria. Twenty five (96.1%) patients had isolated prolactinomas whereas only 1 (3.9%) patient had a multiple endocrine neoplasia type 1. The majority of the patients had macroprolactinomas (n=22, 84.6%) and only 4 (15.4%) showed microprolactinomas. Median serum PRL levels were 52.4 ng/ml (38.3-263.8) for micro- and 1025.0 ng/ml (511.5-4396.5) for macroprolactinomas (p=0.002).

Prevalence of anemia

Mean hemoglobin at diagnosis of prolactinoma was slightly lower than in the last visit of the patients (13.8 ± 1.3 g/dl vs 14.3 ± 1.0 g/dl; ns). No difference in terms of WBC and platelet counts was found. At diagnosis of prolactinoma, normocytic and normochromic anemia was present in 9 (34.6%) patients. Mean Hb value in anemic and non-anemic patients was 12.2 ± 0.5 g/dl and 14.5 ± 0.7 g/dl (p<0.001), respectively. In anemic patients the degree of anemia was always mild (Hb >11 g/dl). Macroprolactinoma patients showed lower Hb level than patients bearing microprolactinomas (13.5 ± 1.2 g/dl vs 15.1 ± 0.9 g/dl, p<0.05) (figure 1). None of the four patients with microprolactinomas exhibited anemia. The presence of anemia was not associated with age of the patients or serum PRL levels at diagnosis of prolactinomas.

Anemia and hypogonadism

Central hypogonadism was diagnosed in 14 (53.8%) patients, all of them with macroprolactinomas. Serum testosterone levels were significantly lower in macro- than in microprolactinoma patients (176.5 ± 107.7 ng/dl vs 441.0 ± 142.8 ng/dl, p<0.001). The presence of anemia was significantly associated with the involvement of gonadal (p=0.013) axis. Hb was significantly lower in hypogonadic compared with normogonadic patients (13.3 ± 1.2 g/dl vs 14.6 ± 1.4 g/dl, p<0.05). In addition, Hb was positively correlated (p<0.05) with serum testosterone in the whole group of male patients. However, when considering only hypogonadic men, Hb value was only positively correlated with FSH (r=0.732; p=0.004). No correlation between Hb and testosterone and gonadotropins in the normogonadic male patients was found. No correlation between Hb and serum PRL levels was found.

Anemia and hypopituitarism

Hypopituitarism was present in 20 (76.9%) patients. Partial hypopituitarism was identified in 13 (50%) patients, whereas total hypopituitarism was diagnosed in 7 (26.9%) patients. Hb value was significantly lower in patients with total hypopituitarism compared with partial hypopituitarism (12.4 ± 1.0 g/dl vs 14.0 ± 1.2 g/dl, p=0.007) (figure 2). A positive and significant (p=0.007) association between the presence of anemia and the number of affected pituitary axes was found. Hb level was positively correlated with both FT4 (r=0.675; p=0.002)

and cortisol ($r=0.542$; $p=0.009$), but not with PRL and IGF 1. The presence of anemia was associated to the involvement of thyroid ($p=0.001$) and adrenal ($p=0.001$) axes. A logistic regression analysis performed to study the influence of age, the presence of hypogonadism or hypopituitarism, and serum levels of several hormones (PRL, testosterone, cortisol, FT4 and IGF 1) on the presence of anemia at diagnosis of prolactinoma in men showed that only FT4 (OR 0.231; 95% C.I. 0.066-0.811, $p=0.02$), cortisol (OR 0.809; 95% C.I. 0.679-0.965, $p=0.018$) and the presence of total hypopituitarism (OR 20.0; 95% C.I. 1.68-238.63, $p=0.018$) were significantly related to the presence of anemia.

Discussion

Our results show that anemia is not an uncommon finding in men with prolactinomas. In fact, anemia (Hb <13 g/dl) at diagnosis of prolactinomas was documented in more than one-third (34.6%) of our patients. The degree of anemia was always mild (Hb >11 g/dl). Anemia was always linked to the presence of macroprolactinoma and more frequently associated with total hypopituitarism.

An association between anemia and pituitary adenoma has been identified, mainly in men (5,6). In a retrospective analysis performed in 197 patients (100 men) older than 50 years of age with pituitary adenomas 31 (46.3%) of 67 men with low serum concentrations of testosterone were anemic (hematocrit < 40% for men). More recently, a retrospective study in a group of 36 consecutive male patients with macroprolactinomas showed that 16 (44.4%) male patients presented with anemia (Hb<13 g/dl). The prevalence of anemia in our study was slightly lower (~35%), however, this percentage might reflect more accurately the prevalence of anemia in men with prolactinomas because in our study we did not exclude male patients with microprolactinomas. This subgroup of patients was 15.4% and none of them showed anemia.

Testosterone modulates Hb levels in men by means of stimulating hematopoiesis by several mechanisms, such as increasing erythropoietin production and the number of erythropoietin-responsive cells (9). In this setting, low testosterone levels have been associated with anemia in both middle-aged and older men (10, 11). On the other hand, mild anemia has been described in both primary and secondary hypogonadism (12,13). Pituitary tumors are the most common causes of secondary hypogonadism in men. Among them, prolactinomas are the most frequent hormone-secreting pituitary tumors, accounting for about 60%. In a recent study Shimon et al. (6) reported that anemia associated with macroprolactinomas in men was related to hypogonadism and tumor size, improving after appropriate therapy which normalized both PRL and testosterone. Our study confirmed these results, i.e., the presence of anemia was associated with the involvement of gonadal axis which was present in macroprolactinomas.

Apart from hypogonadism other hormonal deficiencies such as hypothyroidism and adrenal insufficiency might explain the existence of anemia in patients with hypopituitarism (14).

Anemia is diagnosed in 23-60% of hypothyroid patients and the prevalence of hypothyroidism in anemic patients is about 20%. Moreover, hypothyroidism associated anemia is usually reversible with increasing Hb after hormone replacement therapy with levothyroxine (15,16). Studies *in vitro* have shown that thyroid hormones enhance hypoxia-induced erythropoietin production (17). Something similar occurs in patients with adrenal insufficiency. Adrenal insufficiency is often accompanied by anemia. This association has been reported in both primary (18) and secondary (19) adrenal insufficiency. Cortisol stimulates erythroid colony growth and it has been suggested that this hormone might play a role in the physiological regulation of human erythropoiesis (20).

Our study is the first one that evaluates and analyzes the relationship between anterior pituitary function and Hb in a significant number of men with prolactinomas. Our findings suggest that the presence of anemia in these patients is a marker of hypopituitarism and not only of hypogonadism. This fact is important due primarily to the therapeutic implications related to the introduction of hormone replacement therapy at diagnosis. Our results are limited by the retrospective nature of the study and the relatively low number of included patients.

In conclusion, the presence of anemia, usually mild (Hb >11 g/dl), is not an uncommon finding (~35%) in men with a recent diagnosis of prolactinoma. This usually indicates the existence of a macroprolactinoma associated with panhypopituitarism.

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Figures

Figure 1. Hemoglobin values at diagnosis in both macro- and microprolactinomas in male patients. The horizontal line corresponds to the hemoglobin level consistent with anemia.

*p<0.05

Figure 2. Hemoglobin values in male patients with total or partial hypopituitarism and with normal pituitary function at diagnosis of prolactinomas in male patients. The horizontal line corresponds to the hemoglobin level consistent with anemia.

** $p < 0.01$