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Pedro Iglesias, José Carlos Castro, Juan J Díez. CLINICAL SIGNIFICANCE OF ANEMIA ASSOCIATED WITH PROLACTIN-SECRETING PITUITARY TUMORS IN MEN. *International Journal of Clinical Practice*, 2011, 65 (6), pp.669. 10.1111/j.1742-1241.2011.02662.x . hal-00640462

HAL Id: hal-00640462

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Submitted on 12 Nov 2011

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Journal:	<i>International Journal of Clinical Practice</i>
Manuscript ID:	IJCP-01-11-0019.R1
Wiley - Manuscript type:	Original Paper
Date Submitted by the Author:	09-Feb-2011
Complete List of Authors:	Iglesias, Pedro Castro, José Carlos; Hospital General, Endocrinology Díez, Juan J; Hospital Ramón y Cajal, Endocrinology
Specialty area:	

SCHOLARONE™
Manuscripts

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

(Revised version-R1)

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Keywords: Anemia, hemoglobin, hypogonadism, hypopituitarism, men, testosterone

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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

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3 was made either immunohistologically after surgery or meeting the following clinical diagnostic
4 criteria: a mean serum PRL level ≥ 35 ng/ml associated with pituitary tumor (≤ 10 mm) in the
5 computed tomography (CT) or magnetic resonance imaging (MRI) for microprolactinomas and a
6 mean serum PRL level ≥ 200 ng/ml and a pituitary tumor (>10 mm) in CT or MRI study for
7 macroprolactinomas. None of the patients took drugs known to modify PRL concentrations at
8 the moment of the study.
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12 13 *Analytical variables*

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16 In every patient we assessed the following analytical data at the time of prolactinoma
17 diagnosis: hemoglobin (Hb) concentration, hematocrit, mean corpuscular volume (MCV), mean
18 corpuscular hemoglobin (MCH), white blood cell (WBC), platelet counts and baseline hormonal
19 levels of concentrations [thyrotropin, TSH (N: 0.350-4.950 mU/l); free thyroxine, FT4 (N: 0.70-
20 1.48 ng/dl); follicle stimulating hormone, FSH (N: 3.5-12.5 mU/ml); luteinizing hormone, LH (N:
21 2.4-12.6 mU/ml); testosterone (N: 300-900 ng/dl); cortisol (N: 5-25 mcg/dl); and insulin-like
22 growth factor type 1, IGF 1 (N: 109-284 ng/ml)]. Anemia was defined by using the World Health
23 Organization criteria (Hb level <13 g/dl in men) (7). We also assessed the presence or absence
24 of hypopituitarism at diagnosis registering type and number of pituitary deficiencies. Central
25 hypogonadism was defined when serum testosterone was lower than 300 ng/dl and low or low-
26 normal gonadotropin levels (8). Hb, hematocrit, and hormone measurements were performed in
27 the laboratories of each hospital using standard automated blood count analyzer,
28 radioimmunoassay, immunoradiometric assay or enzymoimmunometric assay methods.
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37 *Statistical analysis*

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

57 *Clinical features and analytical data*

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3 A group of 26 men (age 38.8 ± 15.4 years) with prolactinomas was evaluated. Twelve
4 prolactinomas (46.2%) were diagnosed immunohistologically. The rest of the patients (n=14,
5 53.8%) met all the clinical diagnostic criteria. Twenty five (96.1%) patients had isolated
6 prolactinomas whereas only 1 (3.9%) patient had a multiple endocrine neoplasia type 1. The
7 majority of the patients had macroprolactinomas (n=22, 84.6%) and only 4 (15.4%) showed
8 microprolactinomas. Median serum PRL levels were 52.4 ng/ml (38.3-263.8) for micro- and
9 1025.0 ng/ml (511.5-4396.5) for macroprolactinomas ($p=0.002$).

14 *Prevalence of anemia*

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18 Mean hemoglobin at diagnosis of prolactinoma was slightly lower than in the last visit of
19 the patients (13.8 ± 1.3 g/dl vs 14.3 ± 1.0 g/dl; ns). No difference in terms of WBC and platelet
20 counts was found. At diagnosis of prolactinoma, normocytic and normochromic anemia was
21 present in 9 (34.6%) patients. Mean Hb value in anemic and non-anemic patients was $12.2 \pm$
22 0.5 g/dl and 14.5 ± 0.7 g/dl ($p<0.001$), respectively. In anemic patients the degree of anemia
23 was always mild (Hb >11 g/dl). Macroprolactinoma patients showed lower Hb level than patients
24 bearing microprolactinomas (13.5 ± 1.2 g/dl vs 15.1 ± 0.9 g/dl, $p<0.05$) (figure 1). None of the
25 four patients with microprolactinomas exhibited anemia. The presence of anemia was not
26 associated with age of the patients or serum PRL levels at diagnosis of prolactinomas.

31 *Anemia and hypogonadism*

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35 Central hypogonadism was diagnosed in 14 (53.8%) patients, all of them with
36 macroprolactinomas. Serum testosterone levels were significantly lower in macro- than in
37 microprolactinoma patients (176.5 ± 107.7 ng/dl vs 441.0 ± 142.8 ng/dl, $p<0.001$). The presence
38 of anemia was significantly associated with the involvement of gonadal ($p=0.013$) axis. Hb was
39 significantly lower in hypogonadic compared with normogonadic patients (13.3 ± 1.2 g/dl vs 14.6
40 ± 1.4 g/dl, $p<0.05$). In addition, Hb was positively correlated ($p<0.05$) with serum testosterone in
41 the whole group of male patients. However, when considering only hypogonadic men, Hb value
42 was only positively correlated with FSH ($r=0.732$; $p=0.004$). No correlation between Hb and
43 testosterone and gonadotropins in the normogonadic male patients was found. No correlation
44 between Hb and serum PRL levels was found.

50 *Anemia and hypopituitarism*

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54 Hypopituitarism was present in 20 (76.9%) patients. Partial hypopituitarism was
55 identified in 13 (50%) patients, whereas total hypopituitarism was diagnosed in 7 (26.9%)
56 patients. Hb value was significantly lower in patients with total hypopituitarism compared with
57 partial hypopituitarism (12.4 ± 1.0 g/dl vs 14.0 ± 1.2 g/dl, $p=0.007$) (figure 2). A positive and
58 significant ($p=0.007$) association between the presence of anemia and the number of affected
59 pituitary axes was found. Hb level was positively correlated with both FT4 ($r=0.675$; $p=0.002$)
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3 and cortisol ($r=0.542$; $p=0.009$), but not with PRL and IGF 1. The presence of anemia was
4 associated to the involvement of thyroid ($p=0.001$) and adrenal ($p=0.001$) axes. A logistic
5 regression analysis performed to study the influence of age, the presence of hypogonadism or
6 hypopituitarism, and serum levels of several hormones (PRL, testosterone, cortisol, FT4 and
7 IGF 1) on the presence of anemia at diagnosis of prolactinoma in men showed that only FT4
8 (OR 0.231; 95% C.I. 0.066-0.811, $p=0.02$), cortisol (OR 0.809; 95% C.I. 0.679-0.965, $p=0.018$)
9 and the presence of total hypopituitarism (OR 20.0; 95% C.I. 1.68-238.63, $p=0.018$) were
10 significantly related to the presence of anemia.
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15 Discussion

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19 Our results show that anemia is not an uncommon finding in men with prolactinomas. In
20 fact, anemia (Hb <13 g/dl) at diagnosis of prolactinomas was documented in more than one-
21 third (34.6%) of our patients. The degree of anemia was always mild (Hb >11 g/dl). Anemia was
22 always linked to the presence of macroprolactinoma and more frequently associated with total
23 hypopituitarism.
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28 An association between anemia and pituitary adenoma has been identified, mainly in
29 men (5,6). In a retrospective analysis performed in 197 patients (100 men) older than 50 years
30 of age with pituitary adenomas 31 (46.3%) of 67 men with low serum concentrations of
31 testosterone were anemic (hematocrit < 40% for men). More recently, a retrospective study in a
32 group of 36 consecutive male patients with macroprolactinomas showed that 16 (44.4%) male
33 patients presented with anemia (Hb<13 g/dl). The prevalence of anemia in our study was
34 slightly lower (~35%), however, this percentage might reflect more accurately the prevalence of
35 anemia in men with prolactinomas because in our study we did not exclude male patients with
36 microprolactinomas. This subgroup of patients was 15.4% and none of them showed anemia.
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43 Testosterone modulates Hb levels in men by means of stimulating hematopoiesis by
44 several mechanisms, such as increasing erythropoietin production and the number of
45 erythropoietin-responsive cells (9). In this setting, low testosterone levels have been associated
46 with anemia in both middle-aged and older men (10, 11). On the other hand, mild anemia has
47 been described in both primary and secondary hypogonadism (12,13). Pituitary tumors are the
48 most common causes of secondary hypogonadism in men. Among them, prolactinomas are the
49 most frequent hormone-secreting pituitary tumors, accounting for about 60%. In a recent study
50 Shimon et al. (6) reported that anemia associated with macroprolactinomas in men was related
51 to hypogonadism and tumor size, improving after appropriate therapy which normalized both
52 PRL and testosterone. Our study confirmed these results, i.e., the presence of anemia was
53 associated with the involvement of gonadal axis which was present in macroprolactinomas.
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Apart from hypogonadism other hormonal deficiencies such as hypothyroidism and
adrenal insufficiency might explain the existence of anemia in patients with hypopituitarism (14).

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3 Anemia is diagnosed in 23-60% of hypothyroid patients and the prevalence of hypothyroidism in
4 anemic patients is about 20%. Moreover, hypothyroidism associated anemia is usually
5 reversible with increasing Hb after hormone replacement therapy with levothyroxine (15,16).
6 Studies *in vitro* have shown that thyroid hormones enhance hypoxia-induced erythropoietin
7 production (17). Something similar occurs in patients with adrenal insufficiency. Adrenal
8 insufficiency is often accompanied by anemia. This association has been reported in both
9 primary (18) and secondary (19) adrenal insufficiency. Cortisol stimulates erythroid colony
10 growth and it has been suggested that this hormone might play a role in the physiological
11 regulation of human erythropoiesis (20).
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18 Our study is the first one that evaluates and analyzes the relationship between anterior
19 pituitary function and Hb in a significant number of men with prolactinomas. Our findings
20 suggest that the presence of anemia in these patients is a marker of hypopituitarism and not
21 only of hypogonadism. This fact is important due primarily to the therapeutic implications related
22 to the introduction of hormone replacement therapy at diagnosis. Our results are limited by the
23 retrospective nature of the study and the relatively low number of included patients.
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28 In conclusion, the presence of anemia, usually mild (Hb >11 g/dl), is not an uncommon
29 finding (~35%) in men with a recent diagnosis of prolactinoma. This usually indicates the
30 existence of a macroprolactinoma associated with panhypopituitarism.
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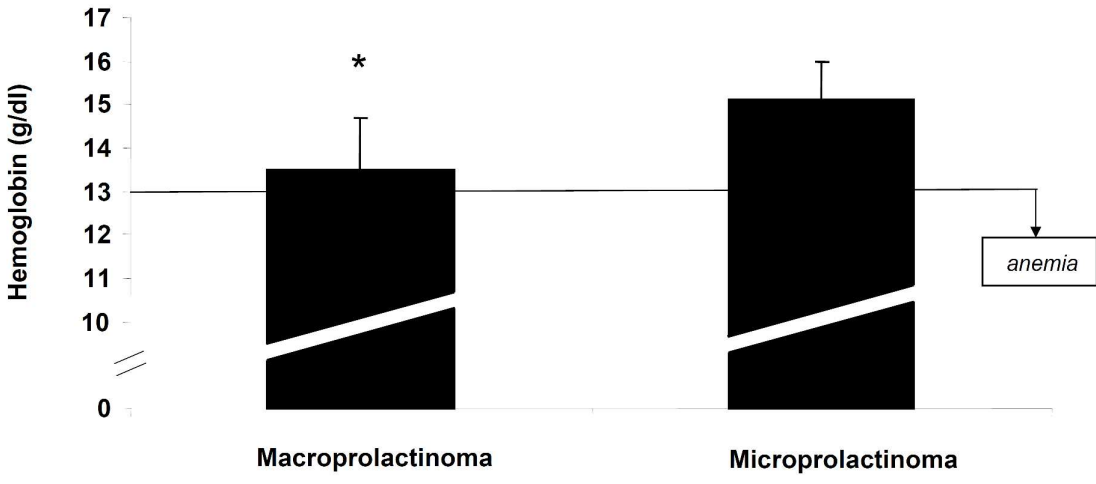
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Figures

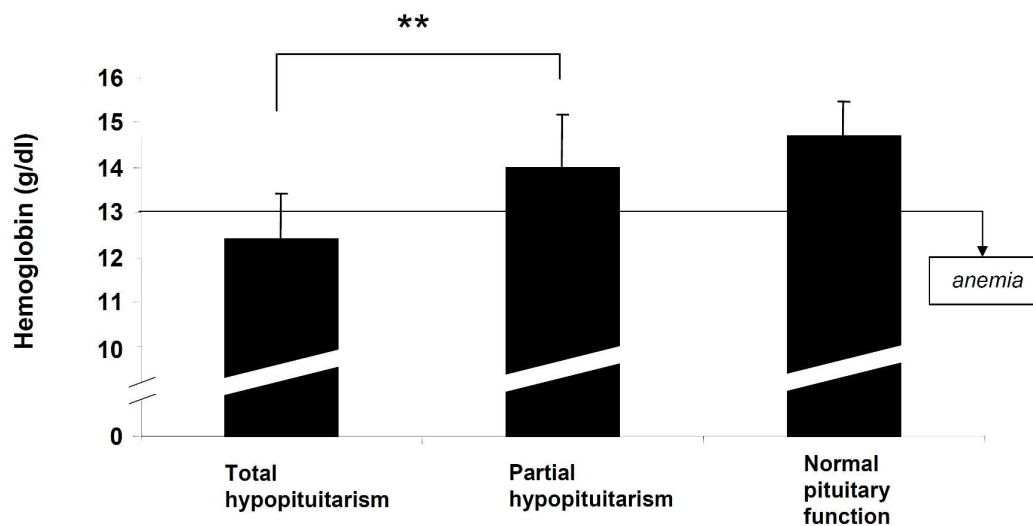
Figure 1. Hemoglobin values at diagnosis in both macro- and microprolactinomas in male patients. The horizontal line corresponds to the hemoglobin level consistent with anemia.



* $p < 0.05$

Review Only

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

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