Anemia, testosterone, and pituitary adenoma in men

DILANTHA B. ELLEGALA, M.D., TORD D. ALDEN, M.D., DANIEL E. COUTURE, M.D., MARY L. VANCE, M.D., NICHOLAS F. MAARTENS, F.R.C.S., AND EDWARD R. LAWS, JR., M.D.

Departments of Neurological Surgery and Internal Medicine, University of Virginia Health Sciences Center, Charlottesville, Virginia; and Department of Neurosurgery, The Radcliffe Infirmary, Oxford, United Kingdom

Object. Older men with clinically nonfunctioning pituitary tumors have been noted to be anemic, to have hypopituitarism, and to have low serum levels of testosterone. The authors hypothesized that men with pituitary adenomas and hypogonadism have a physiologically related decrease in hematocrit.

Methods. A retrospective analysis was conducted of 216 patients older than 50 years of age who harbored pituitary adenomas. In 100 men serum testosterone levels and a complete blood (cell) count (CBC) were obtained before treatment; a CBC was also acquired in a series of women with pituitary adenomas. Using clinical laboratory standards, anemia was defined as a hematocrit less than 40% in men and less than 35% in women.

Thirty-one (46.3%) of 67 men with low serum concentrations of testosterone were anemic. In men with low levels of testosterone, the average hematocrit was 39.9%, compared with 45.6% for men with normal testosterone levels (p < 0.001). Men with macroadenomas were most likely to have both anemia and a low serum concentration of testosterone. Anemia was associated with a low level of testosterone, adjusting for tumor size (odds ratio 19, 95% confidence interval 4.86–77.03). Of patients with anemia, 84% were men and 16% were women (p < 0.001). The prevalence of anemia in women was low and was not correlated with tumor size. Men receiving testosterone replacement therapy had a significantly higher hematocrit value than men with low or normal testosterone levels.

Conclusions. These findings support a direct relationship between serum testosterone levels and hematopoiesis in men, and demonstrate that hematopoiesis is compromised in men who have low concentrations of testosterone due to a pituitary adenoma.

KEY WORDS • anemia • testosterone • pituitary tumor • hypogonadism

Pituitary adenomas account for 10 to 18% of all primary intracranial neoplasms. The majority of large clinically nonfunctioning pituitary tumors are associated with hypopituitarism, a clinical hallmark of which, particularly in men, is pallor. A large proportion of these men have low serum testosterone levels. It is known that testosterone and its derivatives have stimulating effects on erythropoiesis. Testosterone stimulates pluripotent stem cells and increases colony-forming unit–erythroid production in vitro. Androgens stimulate heme synthesis and increase iron incorporation in polycythemic mice. Testosterone and 5β-dihydrotestosterone increase plasma erythropoietin levels in anemic patients. More recently, testosterone has been shown to alleviate the anemia caused by combined hormone blockade therapy. Additionally, hypogonadism has been associated with anemia, and testosterone replacement restores the number of red blood cells.

We have observed that some men with pituitary tumors (usually older men with nonfunctioning adenomas) display clinical signs (pallor) and symptoms (fatigue) of anemia. We hypothesized that hypogonadism in men with pituitary adenomas is associated with anemia and, if this is the case, in men with low serum testosterone levels the hematocrit should be abnormally low and similar to that of a control group of postmenopausal women. Furthermore, we proposed that among the circulating hormones, testosterone is a critical hormone affecting erythropoiesis in men.

Clinical Material and Methods

A retrospective analysis was performed of all men and women 50 years of age or older who underwent surgery for pituitary lesions, which was performed by the senior author (E.R.L.) at the UVA Health Sciences Center between June 1994 and December 1998. Preoperative serum levels of testosterone, PRL, cortisol, TSH, total T4, IGF-I, ACTH, LH, and FSH as well as α subunit and a CBC (hematocrit, hemoglobin, mean corpuscular volume, and platelets) were routinely assessed. The standard for anemia was taken as a hematocrit that was less than 60% in men and less than 55% in women in accordance with standards of the UVA Clinical Laboratory. Total serum testosterone levels lower than 310...
ng/dl were considered below normal for men 50 to 61 years of age and levels lower than 210 ng/dl were deemed abnormal for men older than 61 years. Normal values for other hormones were as follows: TSH 0.4 to 6 μIU/ml; total T 4.5 to 10.9 μg/dl; age-matched IGF-I 71 to 290 ng/ml; cortisol 2 to 18 μg/dl; ACTH less than 3.6 ng/ml; α subunit less than 3.6 ng/ml; LH 0.4 to 8.4 mIU/ml; FSH 2.2 to 10.9 mIU/ml; PRL 1.8 to 19.2 μg/dl; and PRL less than 20 ng/ml (according to the standards of the UVA Clinical Laboratory).

Statistical Analysis

Statistical analysis was performed using commercially available software (STATISTICA for Windows, 1998; StatSoft Inc., Tulsa, OK). The chi-square test was used to compare population proportions. Linear regression analysis was used to explore correlations between various hormone levels and measures of anemia. Analysis of covariance was used to compare groups, adjusting for age. Multiple logistic regression analysis with calculation of odds ratios and associated confidence intervals were calculated to explore predictors of anemia and low levels of testosterone. The level for statistical significance was set at a probability value less than 0.05.

Results

Two hundred sixteen patients older than 50 years of age who harbored pituitary lesions were surgically treated by one neurosurgeon (E.R.L.). Reliable information on pituitary function and a preoperative CBC were available in 197 of these patients. Of these, 100 patients (50.8%) were men and 97 (49.2%) were women. The average age of the men was 61.3 years (range 50–86 years) and that of the women was 60.6 years (range 50–83 years). The percentages of patients with macroadenomas (lesions > 10 mm in diameter) were 82% for men and 63% for women (Table 1 and Fig. 1). The mean values for hemoglobin, hematocrit, mean corpuscular volume, platelets, and serum hormones for postmenopausal women, men with low testosterone levels, and men with normal testosterone levels are shown in Table 1. Thirty-three of the 100 men had normal serum testosterone levels. Of these 33 men, 11 were receiving TRT. The mean hematocrit for men with normal testosterone levels who were not receiving TRT was 44.4% and that for men with normal testosterone levels who were receiving TRT was 48.2% (p < 0.001). The mean hematocrit for men with low testosterone levels was 39.9%. The mean hematocrit for postmenopausal women harboring pituitary tumors was 40.1%. The mean hematocrit for men with low testosterone levels was significantly lower than that measured in men with normal serum levels of testosterone (p < 0.0001). Overall, 31 (46.3%) of 67 men with low serum testosterone levels were anemic. Additionally, men with normal concentrations of testosterone who harbored a pituitary tumor had higher hematocrits than postmenopausal women who had a pituitary adenoma (p < 0.0001). There was no difference in hematocrit between men with low serum concentrations of testosterone and postmenopausal women. Sixty-seven (67%) of 100 men with pituitary tumors had low serum hematocrits. In all patient groups, the mean corpuscular volume was normal.

Table 2 details the hemoglobin and hematocrit values for postmenopausal women, men with low concentrations of testosterone, men with low testosterone levels while receiving TRT, men with normal levels of testosterone, and men with normal levels of testosterone while receiving TRT, as they relate to tumor size. In 55 men with macroadenomas and low serum concentrations of testosterone, anemia was present in 30 (54.5%). Anemia was independently associated with a low testosterone level (odds ratio 19, 95% confidence interval 4.86–77.03). Of all anemic patients, 84% were men and 16% were women (p < 0.001).

Figure 2 provides a plot of the serum testosterone levels and hematocrit values. Using linear regression analy-
sis, there was a significant correlation between testosterone levels and hematocrit values, and testosterone levels lower than 78 ng/dl were associated with more severe anemia (average hematocrit 38.5%). Using ANCOVA, there were significant effects for both tumor size and TRT (Table 2). There were no significant correlations between the level of other pituitary hormones, such as cortisol, PRL, TSH, total 

\( T_4 \), IGF-I, ACTH, LH, FSH, or \( \alpha \) subunit, and hematocrit value. Although it was not significant, there was a trend toward a significant correlation between patient age and total \( T_4 \) levels (Table 1).

Discussion

In this retrospective review of 197 patients with pituitary tumors, we attempted to ascertain whether the clinical observation of anemia correlates with hypogonadism in men with pituitary adenoma. Our findings demonstrate that the testosterone level is independently correlated with the hematocrit. There is a consistent reduction in hematocrit values in patients with low testosterone levels. Men with low levels of this hormone had hematocrits similar to those of postmenopausal women. The mean corpuscular volume was normal in all groups. There was no significant relationship between other circulating hormone levels and the hematocrit; however, there was a nonsignificant trend toward a correlation of hematocrit with total \( T_4 \) levels and with the age of the patient (Table 1). The lack of correlation between level of thyroid hormones and hematocrit is unexpected, because numerous studies have linked these two variables in the past.\(^5,13,14\) The marginal correlation of patient age with hematocrit demonstrated in this review is not surprising because cross-sectional population studies that have demonstrated a decrease in the hematocrit with increasing age have included much larger cohorts.\(^7\) Previous studies have shown a stepwise decrease in testosterone levels,\(^6,8,15\) especially after the age of 50 years.\(^17\) We did not find a significant correlation between age and testosterone in this population. This lack of correlation may reflect an overriding influence of testosterone on hematopoiesis in this patient population, thus obscuring the effect of age.

### TABLE 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Microadenoma</th>
<th>Macroadenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hb (g/dl)</td>
<td>Hct (%)</td>
</tr>
<tr>
<td>postmenopausal women</td>
<td>13.7</td>
<td>41.2</td>
</tr>
<tr>
<td>men w/ low testosterone levels who are not receiving TRT (60 patients; mean testosterone level 114.3 ng/dl)</td>
<td>14.4</td>
<td>42.7</td>
</tr>
<tr>
<td>men w/ low testosterone levels who are receiving TRT (7 patients; mean testosterone level 170.6 ng/dl)</td>
<td>14.8</td>
<td>44.0</td>
</tr>
<tr>
<td>men w/ normal testosterone levels who are not receiving TRT (22 patients; mean testosterone level 401.7 ng/dl)</td>
<td>16.2</td>
<td>49.1</td>
</tr>
<tr>
<td>men w/ normal testosterone levels who are receiving TRT (11 patients; mean testosterone level 682.7 ng/dl)</td>
<td>17.2</td>
<td>51.3</td>
</tr>
</tbody>
</table>

\(^\star\) p < 0.01 for group and tumor size effects by ANCOVA. Abbreviations: Hb = hemoglobin; Hct = hematocrit.
Anemia, testosterone, and pituitary adenoma

The size of the tumor was significantly and independently associated with the hematocrit. Patients with macroadenomas had lower hematocrits than those with microadenomas. The effect on the hematocrit observed in the presence of macroadenomas may represent a cumulative effect of a global, mild lowering of all pituitary hormones in these patients due to the mass effect of the tumor. This conjectured global effect was not supported by analysis of individual hormones, however; testosterone production is particularly vulnerable to the effects of an expanding intrasellar mass.

As shown in Table 2, men with low testosterone levels and macroadenomas had essentially the same hematocrit values as postmenopausal women with macroadenomas. This supports the hypothesis that testosterone and/or its metabolites are significant determinants of erythropoiesis in men.

Although the correlation between testosterone and hematocrit is evident from these results, the degree of anemia in this group of men was not dramatic. Nevertheless, men with very low testosterone levels (< 78 ng/dl) had a greater reduction in hematocrit values, with an average value of 38.5%. Men who were receiving TRT not only had higher hematocrits than men with low testosterone levels, but they also had higher hematocrit values than men with normal testosterone levels who were not receiving TRT. This interesting finding may be a consequence of the higher-than-normal testosterone levels found in patients receiving TRT. It also supports the idea that recovery of normal testosterone levels found in patients receiving TRT. This supports the hypothesis that testosterone and/or its metabolites are significant determinants of erythropoiesis in men.

The anemia that accompanies chronic disease is usually attributed to chronic inflammation, liver disease, renal disease, and less common causes such as hypothyroidism, rheumatoid arthritis, systemic lupus erythematosus, and human immunodeficiency viral infection. We suggest that hypogonadism in men due to a pituitary adenoma is also a potential cause of normocytic normochromic anemia, and should be considered in the differential diagnosis.

Conclusions

The anemia that accompanies chronic disease is usually attributed to chronic inflammation, liver disease, renal disease, and less common causes such as hypothyroidism, rheumatoid arthritis, systemic lupus erythematosus, and human immunodeficiency viral infection. We suggest that hypogonadism in men due to a pituitary adenoma is also a potential cause of normocytic normochromic anemia, and should be considered in the differential diagnosis.

Acknowledgment

We are grateful to Ms. Barbara Behnke for her expert assistance in the preparation of the manuscript.

References


Manuscript received September 27, 2002. Accepted in final form February 10, 2003.
Address reprint requests to: Edward R. Laws, Jr., M.D., Department of Neurological Surgery, University of Virginia Health Sciences Center, P.O. Box 800212, Charlottesville, Virginia 22908. email: e15g@virginia.edu.