

Pituitary imaging is indicated for the evaluation of hyperprolactinemia

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Objective: To evaluate the signs and symptoms associated with hyperprolactinemia and establish guidelines for a minimal serum PRL level for which pituitary imaging is indicated.

Design: Retrospective study.

Setting: Reproductive endocrinology clinic in a university hospital.

Patient(s): One hundred four consecutive patients with hyperprolactinemia, mean age 30 ± 6.5 (range 19–44) years.

Intervention(s): Classification of clinical symptoms, serum hormone measurements, and pituitary magnetic resonance imaging (MRI).

Main Outcome Measure(s): Incidence of presenting symptoms, serum PRL levels, and pituitary tumor size.

Result(s): Median (range) PRL value was 82.6 ng/mL (25–1,342). Reported symptoms from most to least common were infertility (48%), headaches (39%), oligoamenorrhea (29%), galactorrhea (24%), and visual changes (13%). Hypothyroidism was diagnosed in 2 of 104 (1.9%) patients. Of 86 patients who had pituitary imaging, 23 (26%) had normal findings and 63 (74%) had pituitary tumor; of these, 47 (55% of total imaged) had microadenomas and 16 (19% of total imaged) had macroadenomas. There was a statistically significant association between the tumor size and the PRL level. However, 11% of the patients with microadenomas had PRL levels >200 ng/mL, and 44% of the patients with macroadenomas had PRL levels between 25 and 200 ng/mL.

Conclusion(s): The most common symptoms in the population studied were infertility and headaches. Coexisting thyroid disease was an uncommon finding. Most patients had a pituitary tumor on MRI. Although tumor size correlated with the serum PRL level, some macroadenomas were detected in women with only moderately elevated PRL values. On the basis of these findings, pituitary imaging should be obtained to identify pituitary tumors in all patients with persistently elevated PRL levels. (*Fertil Steril*® 2005;84:181–5. ©2005 by American Society for Reproductive Medicine.)

Key Words: Hyperprolactinemia, prolactin, MRI, hypothyroidism, pituitary tumor, infertility

Hyperprolactinemia is the most common endocrine disorder of the hypothalamic-pituitary axis. It is estimated to occur in 9%–17% of women with reproductive disorders (1, 2). Clinical manifestations of hyperprolactinemia include hypogonadal symptoms (oligoamenorrhea, decreased libido, and infertility), galactorrhea, and symptoms related to mass effect such as headaches and visual changes (2). The differential diagnosis of hyperprolactinemia includes hypothalamic/pituitary tumors, of which the prolactinoma is the most common; ingestion of drugs that deplete dopamine or block its action at the receptor; neurogenic chest wall lesions; hypothyroidism; polycystic ovary syndrome (PCOS); cirrhosis; and end-stage renal failure (3).

Received June 1, 2004; revised and accepted January 4, 2005.

Presented at the 51st Annual Meeting of the Pacific Coast Reproductive Society, April 23–27, 2003, Rancho Mirage, California.

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The standard initial work-up of a patient who presents with an elevated PRL level includes the repeat measurement of PRL with the patient in a fasting state in the morning. If the patient has a persistently elevated PRL level and other causes have been excluded, a hypothalamic/pituitary tumor is postulated and imaging studies are obtained (2, 4). Magnetic resonance imaging (MRI) is considered the most sensitive imaging method for identifying pituitary tumors (5). However, the degree of elevation of serum PRL level that warrants an MRI study is controversial. Some investigators suggest evaluation by MRI only if the PRL level is >100 ng/mL (6). Others recommend an imaging study for all patients with persistently elevated PRL levels when there is no identifiable secondary cause of hyperprolactinemia (2, 3).

The purpose of this study was to evaluate the signs and symptoms associated with hyperprolactinemia and to establish guidelines for a minimal serum PRL level for which pituitary imaging is indicated.

MATERIALS AND METHODS

We reviewed the medical records of female patients with hyperprolactinemia evaluated in the Reproductive Endocri-

nology and Infertility Clinic at the Los Angeles County–University of Southern California Medical Center between 1997 and 2002. All patients with elevated PRL levels (N = 104) were included in the study. Most patients in the study were Hispanic in origin. Mean age in the population studied was 30 ± 6.5 (range 19–44) years. The study was approved by the University of Southern California Health Sciences Institutional Review Board.

Prolactin hormone was measured in all patients in the same laboratory using the same assay (AxSYM System; Abbott Laboratories, Abbott Park, IL). Normal range of the assay was 1–25 ng/mL. If patients were referred to our clinic for hyperprolactinemia, hormone measurements were repeated in our laboratory and that value used in the study. Hyperprolactinemia, defined as a PRL level >25 ng/mL, was confirmed in all patients by repeat measurement in the morning in a fasting nonstressed state without prior intercourse or breast stimulation. Patients were excluded from the study if they did not have a repeat fasting PRL level in the morning or had incomplete work-up. All patients underwent history and physical examinations. Patients were specifically questioned about irregular menses, galactorrhea, headaches, visual changes, and infertility. Physiologic and pharmacologic causes associated with hyperprolactinemia, such as pregnancy, lactation, or drug use, were excluded in all patients. None of the patients in the study reported using drugs associated with hyperprolactinemia.

Baseline measurements of TSH, E_2 , LH, and FSH were obtained using commercial immunoassay kits. MRI of the hypothalamic/pituitary area was obtained after all secondary causes of hyperprolactinemia were excluded. MRI was performed at 1.5 T, in sagittal and coronal planes with 2.5 mm slice thickness without interslice gap. T1-weighted spin-echo images were acquired with repetition time (TR) of 500 ms and echo time (TE) of 15 ms and pre- and postcontrast using 5 cc of gadolinium. Microadenoma was defined as the MRI finding of a pituitary tumor measuring less than 10 millimeters in its greatest diameter; and macroadenoma was defined as a tumor measuring 10 millimeters or more in its greatest diameter. Each MRI was interpreted by one of the four neuroradiologists, all of whom were similarly trained to interpret MRIs and all of whom work in the department of neuroradiology at our institution. Patients who presented with headaches or visual disturbances and all patients with documented macroadenomas were evaluated by formal visual field examinations and by the neurosurgery service.

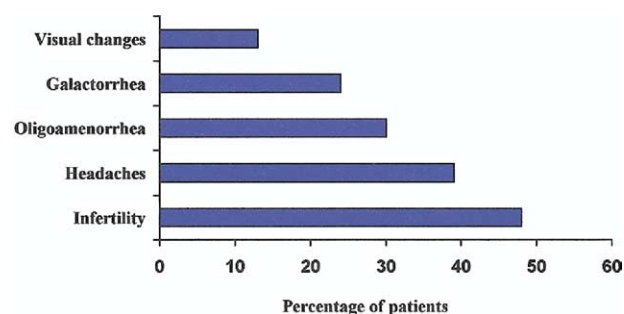
Categorical data were analyzed by Fisher’s exact test. For nonparametric data, Spearman correlation analysis was used. All statistical calculations were performed using SPSS software (SPSS, Chicago, IL). $P < .05$ was considered significant.

RESULTS

The most common clinical symptoms reported by patients with hyperprolactinemia are shown in Figure 1. Infertility

FIGURE 1

Most commonly reported symptoms in patients with hyperprolactinemia.



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was the most common and visual changes the least common symptom, as elicited by history.

The median PRL level was 82.6 ng/mL, with a range of 25–1,342 ng/mL. Of the 104 patients with hyperprolactinemia included in the study, 8 patients were diagnosed with PCOS. The diagnosis of PCOS was made by a combination of a history of chronic anovulation and clinical or laboratory evidence of hyperandrogenism (Ferriman-Gallwey score ≥ 8 or total testosterone level ≥ 60 ng/dL). Other causes of hyperandrogenism were excluded in these 8 patients by evaluating the patients for signs and symptoms of androgen-secreting tumors, late-onset congenital adrenal hyperplasia and Cushing’s syndrome. DHEAS, 17- α -hydroxyprogesterone, and 24-hour urinary free cortisol levels were measured and found to be within the normal ranges.

A diagnosis of premature ovarian failure was established in 2 patients on the basis of a history of amenorrhea, low E_2 , and high LH and FSH levels. With the exclusion of these 2 patients, the median (range) E_2 level was 32.5 (range 20–176) pg/mL.

There were 2 cases of hypothyroidism (1.9%) diagnosed by the finding of low serum thyroxine (T_4) and high serum TSH levels. The PRL hormone levels in these 2 patients were 41 and 83 ng/mL. E_2 , FSH, and LH levels were normal and these patients were treated with thyroid hormone supplementation.

Eighty-six patients underwent MRI testing (Table 1). Normal findings were reported in 23 (26%). Sixty-three patients (74%) had evidence of a pituitary tumor: microadenomas in 47 (55%) and macroadenomas in 16 (19%). There was a statistically significant association between the tumor size and the PRL level ($r = 0.63$, $P < .01$; Fig. 2). There was a statistically significant association between PRL levels >100 ng/mL and the finding of a macroadenoma rather than a microadenoma (odds ratio [OR] = 7.6; 95% confidence interval [CI] = 1.39–55.02; $P < .01$).

TABLE 1**MRI findings in hyperprolactinemic patients stratified by serum prolactin levels.**

PRL levels (ng/mL)	Normal MRI	Microadenoma	Macroadenoma
25–50 (n = 21)	10	10	1
51–100 (n = 27)	12	14	1
101–200 (n = 24)	1	18	5
>201 (n = 14)	0	5	9
Total (n = 86)	23	47	16

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Of those patients with microadenomas, 52% had PRL levels <100 ng/mL. However, 11% of the patients with microadenomas had PRL levels >200 ng/mL, and 44% of the patients with macroadenomas had PRL levels between 25 and 200 ng/mL.

DISCUSSION

We evaluated the signs and symptoms associated with hyperprolactinemia in our clinic over a span of 5 years. During this time, in the population we studied, infertility was the most commonly reported chief complaint. This was not an unexpected finding in patients evaluated in a reproductive endocrinology clinic. However, headaches generally attributed to macroadenomas were also commonly reported by our group of patients regardless of the size of their pituitary tumor. Oligoamenorrhea and/or galactorrhea were present in 53% of patients. Visual changes were rarely reported.

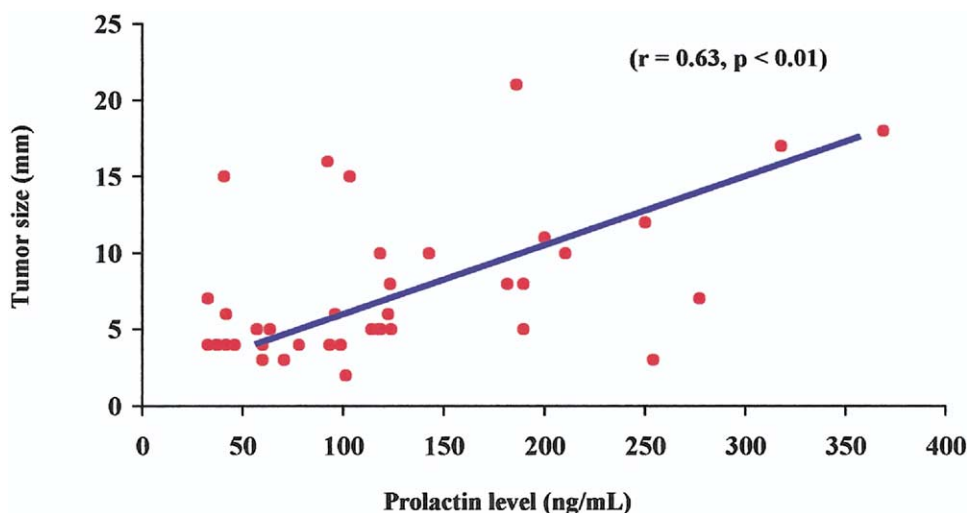
The prevalence of symptoms may vary depending on the population studied and the clinical setting in which the

patient is evaluated. Drange et al. (7) recently reported hypogonadal symptoms in 70% and galactorrhea in 49% of patients with prolactinomas who were treated at an internal medicine/endocrinology tertiary referral center for the evaluation of pituitary tumors. Similarly, headaches and visual changes were more common in patients evaluated in a neurosurgery service (8).

Our findings suggest that hypothyroidism is an uncommon finding among patients with hyperprolactinemia. Although screening for hypothyroidism is considered one of the most important parts of the work-up of hyperprolactinemia, the incidence of hypothyroidism in our patient population was very small. Similar to our finding of 1.9%, previous publications have reported an incidence of hypothyroidism in 1.1% (9), 2% (10), and 3% (11) of patients with elevated PRL levels. Raber et al. (12) recently measured PRL levels in 927 consecutive nonpregnant and nonlactating female hypothyroid patients defined as having a TSH >4.0 mIU/L. Hyperprolactinemia was documented in 7% of the patients.

FIGURE 2

Correlation between the pituitary tumor size and serum PRL level (ng/mL).



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These data were not corrected for patients taking medications that may increase PRL levels, thus possibly overestimating the relationship between elevated TSH levels with elevated PRL levels. In light of these findings, thyroid disease is rarely the etiology of elevated circulating PRL levels.

Our data indicate that most patients with elevated PRL levels have a pituitary tumor (74% of those who underwent MRI). Microadenomas in this population were more common than macroadenomas (55% vs. 19%), a finding in agreement with previous reports (6, 13, 14). Overall, there was a positive correlation between tumor size and PRL level. Microadenomas were more commonly observed with PRL levels <200 ng/mL, and macroadenomas with PRL levels >100 ng/mL. However, there was overlap in PRL values between these two diagnoses: 2 patients with macroadenomas had PRL levels <100ng/mL and 5 patients with microadenomas had PRL levels >200 ng/mL. A PRL-producing tumor is the most likely diagnosis in the latter situation, although a nonprolactin-secreting tumor also can lead to elevations in circulating PRL levels (by compressing the pituitary stalk, leading to suppression of PRL-inhibiting factor) (4). The patient with a non-PRL-producing tumor usually requires neurosurgery, whereas the patient with a PRL-producing tumor is treated medically (8).

A discrepancy between the tumor size and the PRL level may also be due to the lactotroph cell activity within the tumor. This might also be the case in macroadenomas with large cystic parts that are not responsive to dopamine agonist therapy (16). A tumor can secrete very high levels of PRL hormone, resulting in an assay “hook effect” where the results are reported incorrectly as low (17, 18). Conversely, some microadenomas may be particularly efficient in producing PRL hormone or they may secrete macroprolactin defined as the increased secretion of the “big big” PRL isoform (13, 15).

Twenty-three patients with no evidence of tumor or other pathologic causes of hyperprolactinemia had elevated serum PRL. Twelve of these patients had PRL levels between 51 and 100 ng/mL and one of these patients presented with a PRL level of 128 ng/mL. All other causes of hyperprolactinemia were excluded in these patients. The most likely diagnosis in these patients is macroprolactinemia (13, 15).

The hyperprolactinemia associated with PCOS is thought to be secondary to an imbalance in androgen production, possible alterations in dopamine secretion, and/or chronic hyperestrogenism (19–21). However, we found evidence of a pituitary tumor in 5 of 8 patients with PCOS. We therefore suggest pituitary imaging for PCOS patients with persistent elevation of serum PRL levels.

Patients included in this study were mostly Hispanic in origin. However, it is unlikely that genetic factors impact on the development of pituitary tumors; our findings should be

applicable to other ethnic groups with the same presentation. Whereas some of the patients in our study were referred to our clinic specifically for hyperprolactinemia, the high prevalence of pituitary tumors in our study was similar to other studies (6, 13). Thus, findings from this population may represent the standards found by most physicians in practice.

We conclude from these findings that even with PRL values that are just outside the normal range, pituitary tumors can be present. Therefore, pituitary imaging is recommended in all patients with persistently elevated PRL levels, regardless of the value.

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