Screening By Magnetic Resonance Imaging May Be Performed Even In Patients With Mild-Moderate Hyperprolactinemia

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OBJECTIVE: To evaluate the association between the degree of hyperprolactinemia and the possibility of presenting a pituitary adenoma with magnetic resonance imaging. In addition, a threshold value for prolactin level was studied in order to predict micro/macroadenoma.
STUDY DESIGN: A total of 43 patients from a tertiary center, with persistent hyperprolactinemia were retrospectively evaluated. Only patients with a prolactin level more than 20ng/mL with two consecutive analyses were undertaken. Magnetic resonance imaging (MRI) was performed to all cases.
RESULTS: Of the 43 cases, microadenoma and macroadenoma was observed in 14 (32.6%) and 1 (%2.3) patient, respectively. The mean levels of PRL among patients with normal pituary imaging and microadenomas were similar. The unique case with macroadenoma had a PRL level of 56.2ng/mL. When the patients (n=39) were enrolled according to PRL levels, such as <100 ng/mL (n=33) or ≥100 ng/mL (n=6), the possibility of carrying a microadenoma was found to be 33.3% and 50%, respectively (p>0.5).
CONCLUSION: There is no consensus for the cut-off PRL level to predict micro/macroadenoma in patients with persistent hyperprolactinemia. According to limited data, micro/macroadenoma may be presented even in PRL levels less than 100ng/ml. Therefore, the possibility of micro/macroadenoma should not be underestimated in patients with mild-moderate hyperprolactinemia according to the available literature.
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Key Words: Prolactin, Magnetic resonance imaging, Microadenoma, Macroadenoma

Hyperprolactinemia is the most common endocrine disorder of the hypothalamic-pituitary axis and estimated to be found in 9%–17% of women with reproductive disorders[1]. The oligomenorrhea, decreased libido, galactorrhea, headaches and visual changes may be noted in cases with hyperprolactinemia[2]. Although the hypothalamic/pituitary tumor seems to be one of the most common cause, the intake of dopamine antagonist drugs, neurogenic chest wall lesions, hypothyroidism, polycystic ovary syndrome (PCOS), cirrhosis, and end-stage renal failure may be associated with hyperprolactinemia[3].

The standard initial work-up of a patient who presents with an elevated PRL level includes the repeat measurement of prolactin (PRL) in a fasting state in the morning. During recurrent measurement, thyroid functional tests should be evaluated at the same time. In the presence of persistent hyperprolactinemia with normal thyroid functions, imaging of the pituitary gland is recommended [1,2]. In this manner, magnetic resonance imaging (MRI) is considered to be the most sensitive imaging method for identifying pituitary tumors[4]. However, there is paucity of data whether is there a threshold value for serum PRL level which warrants an MRI study to present a micro or macroadenoma. Although ≥100ng/mL is the most accepted threshold for performing a MRI study, there is no consensus for the exact value. In this study, we evaluated the association between PRL levels and possibility of presenting a micro/macroadenoma with MRI of the pituitary gland.

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Materials and Methods

In this study, 7494 consecutive cases were evaluated whose PRL levels were analyzed due to oligomenorrhea, galactorrhea, infertility or other gynecological disorders in Hacettepe University, School of Medicine, Department of Obstetrics and Gynecology, between January 2003 and December 2005. Of them, 370 patients found to have a persistent hyperprolactinemia with confirmed fasting PRL levels more than 20ng/mL. However, only 43 of 370 patients found to have a computer recorded MRI results which were finally evaluated.

Prolactin hormone levels were all measured in the same laboratory using the same assay. Normal range of the assay was 1–25 ng/mL. However, in order to obtain a threshold

value, the study group included cases which carry two recurrent high PRL levels more than 20ng/mL. Of note, irrespective from the initial examination, the secondary analyses of the serum PRL were all performed in fasting state.

Magnetic resonance imaging 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 as reported elsewhere[2]. 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[2]. Student's T, Fisher's exact and Spearman correlation tests were performed for the statistical analysis. All statistical calculations were performed using SPSS software (SPSS 13.0, Chicago, IL) and P<.05 was considered to be significant.

Results

The median age of the 43 patients were 30.2±6.4 (y). The median PRL level tested in whole group was 69.7 ng/ml with a range of 24.4-199.6 ng/ml. All the cases underwent MRI study of the pituitary gland. Of the 43 patients, 25 (58.1%) had normal findings. In the remaining, microadenoma and macroadenoma was observed in 14 (32.6%) and 1 (%2.3) patient, respectively. Of interest, 3 patients (7.0%) found to have disorders rather than hyperprolactinoma (empty cell syndrome, hyperplasia and non-prolactin secreting tumour).

The mean levels of PRL among patients with normal pituary imaging and microadenomas were similar (62.6±46.6 vs. 69.3±33.9 ng/mL, respectively; p>.05). The unique case with macroadenoma had a PRL level of 56.2ng/mL. In addition, no correlation was observed between PRL values and the presence of an adenoma (r=0.22, p=0.9) with MRI. When the patients (n=39) were enrolled according to PRL levels, such as <100 ng/mL (n=33) or ≥100 ng/mL (n=6), the possibility of carrying a microadenoma was found to be 33.3% and 50%, respectively (p>0.5). The distribution of the PRL levels and findings with MRI were listed in Table I.

Discussion

Idiopathic hyperprolactinemia accounts for 30–40% of cases when no pathology is noted with pituitary imaging[5]. Generally, the abnormal prolactin levels spontaneously revert to normal with time in one-third of patients[6]. Certain medications can also cause hyperprolactinemia. Some anti-psychotics, anti-depressants and antiemetics may block the central dopamine system[7], while opiates can stimulate hypothalamic opioid receptors to promote prolactin secretion. Hypothyroidism is another condition that can result in hyperprolactinemia, via stimulation of TRH release and reduced elimination of prolactin from the systemic circulation[8]. Renal and liver failure can also reduce prolactin elimination, resulting in hyperprolactinemia[7]. Neurogenic causes of hyperprolactinemia, such as chest-wall injury and breast stimulation may attenuate dopamine release into the hypophyseal portal circulation which may result with production of high prolactin levels[7]. Of interest, acute stress response and oophorectomy may also cause transient hyperprolactinemia[5].

Prolactinomas account for 25–30% of functioning pituitary tumors[3]. They are predominantly benign and classified according to size. In our study, 41.9% of the patients with persistent hyperprolactinemia found to have any pathology such as adenoma or empty cell syndrome. In a recent study by Bayrak A et al [2], 86 patients were evaluated with MRI due to persistent high PRL levels and 63 (74%) had found to have a pituitary tumor. 47 of 63 (55%) were reported to have microadenomas and 16 (19% of total imaged) had macroadenomas. In concordance, Rand T et al [9] reported a higher incidence of adenomas than the available literature. They examined 55 premenopausal and 19 postmenopausal women and reported an adenoma incidence of 59.4%. The difference in the presence of adenomas related with hyperprolactinemia may be associated with the study groups in which threshold PRL values are varying from 20 to 52ng/ml [2, 9, 10]. One may hypotheses that, when the range is taken widely in the meaning of PRL level, the possibility of determining a micro-macro adenoma may be higher.

Magnetic resonance imaging is a sensitive tool for the investigation of pituitary microadenomas but there is paucity of data for the threshold value to consider a pituitary imaging in patients with hyperprolactinemia. To establish a strategy for

Table I. The distribution of the PRL levels and findings with MRI.

PRL levels (ng/mL)	Normal findings (n)	Microadenoma (n)	Macroadenoma(n)	Non-prolactinoma (n)
<50 (n=17)	13 (76.5%)	4 (23.5%)	0	0
51-100 (n=18)	9 (50.0%)	7 (38.9)	1(5.6%)	1(5.6%)
101-150 (n=5)	1 (20.0%)	3 (60.0%)	0	1 (20.0%)
151-200 (n=3)	2 (66.7%)	0	0	1 (33.3%)

the use of MRI in patients with hyperprolactinemia Rand T et al [9] investigated 74 women with serum prolactin levels above 52 ng/ml for the presence of microadenomas. They found microadenomas in 38 patients (51.3%), macroadenomas in 6 (8.1%) and an infundibular glioma in 1. The remaining 29 patients had a normal pituitary gland (39.2%). They concluded that the probability of the presence of an adenoma increased with rising serum PRL levels and suggested MRI in patients with prolactin levels more than 100 ng/ml[9]. In contrast, Bayrak A et al[2] evaluated 104 women with hyperprolactinemia in a recent retrospective study and referred that pituitary tumors may be observed even in patients with prolactin levels just exceeding the normal range. In our study, the mean PRL levels of the patients with microadenoma and normal pituitary were comparable. Of interest, the unique case of macroadenoma had a PRL value of 56.2 ng/mL and the mean value for microadenomas were 69.3±33.9ng/ml They were both under the 100ng/ml which is preferred for the cut-off value to screen micro/macroadenomas by MRI.

Overall, there is a positive correlation between tumor size and PRL level according to available literature[2,9]. According to Bayrak A et al[2] microadenomas were more commonly observed with PRL levels <200 ng/mL, and macroadenomas with PRL levels >100 ng/mL. However, they documented 2 patients with macroadenomas who had PRL levels <100ng/mL and 5 patients with microadenomas who had PRL levels >200 ng/mL[2]. Rand T et al[9] reported that the mean level in patients with MRI evidence of adenomas was higher than in patients without microadenomas (155.72±131.01 ng/ml vs 110.14±80.86 ng/ml). They concluded that the size of the adenomas was related to the prolactin level and the probability of the presence of an adenoma increased with rising serum prolactin levels. However, in our study we failed to show such a correlation between PRL level and presence of an adenoma with pituitary MRI. A discrepancy between the tumor size and the PRL level may also be due to the lactotroph cell activity within the tumor. In addition very small adenomas may not be visualized during sagittal sections.

As a conclusion, there is no consensus for the cut-off PRL level to predict micro/macroadenoma in patients with persistent hyperprolactinemia. Although, a correlation between PRL levels and the possibility of an adenoma is documented, we failed to show such a relationship which may be associated with limited number of cases in the study. However, according to limited data, micro/macroadenoma may be presented even in PRL levels less than 100ng/ml. Therefore, the possibility of micro/macroadenoma should not be underestimated in patients with mild-moderate hyperprolactinemia according to the available literature. However, these findings should be confirmed with prospective clinical trials consisting larger series.

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