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ORIGINAL ARTICLE

Clinical and radiological findings in macroprolactinemia

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Abstract Hyperprolactinemia is the most common abnormality of the hypothalamic–pituitary axis. The aim of this study was to investigate the clinical and radiological features of patients with macroprolactinemia. The study population consisted of patients with elevated serum prolactin (PRL) concentrations who presented to our Endocrinology outpatient clinic. Detection of macroprolactin (macroPRL) was performed using the polyethylene glycol precipitation method. Patients in which macroPRL made up more than 60% of total PRL levels were stratified into the macroPRL group, while the remaining patients were placed in the monomeric prolactin (monoPRL) group. A total of 337 patients were enrolled with a mean age of 33.8 ± 10.8 (16–66) years and a male/female ratio of 29/308. Eighty-eight of the patients (26.1%) had an elevated macroPRL level. The mean age in the monoPRL group was higher than in the macroPRL group (35.0 ± 10.1 vs. 30.7 ± 9.8, $P = 0.016$). The mean PRL levels (ng/ml) in the macroPRL and monoPRL groups were similar (168.0 ± 347.0 vs. 238.8 ± 584.9, $P = 0.239$). Frequency of amenorrhea, infertility, irregular menses, gynecomastia, and erectile dysfunction were also similar in both groups. More patients in the macroPRL group were asymptomatic compared to the monoPRL group (30.2 vs. 12.0%, $P = 0.006$). Compared to the macroPRL group, the monoPRL group had a higher frequency of galactorrhea (39.2 vs. 57.1%, $P = 0.04$) and abnormal magnetic resonance imaging findings (65.3 vs. 81.1%, $P = 0.02$). Elevated macroPRL levels should be considered a pathological biochemical variant of hyperprolactinemia that may present with any of the conventional symptoms and radiological findings generally associated with elevated PRL levels.

Keywords Prolactin · Hyperprolactinemia · Macroprolactin · Pituitary adenoma

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Introduction

Hyperprolactinemia is the most common abnormality of the hypothalamic–pituitary axis and the most frequent manifestation of functional pituitary adenomas [1]. While physiological elevations occur during pregnancy and lactation, pathological hyperprolactinemia may occur in association with a lactotroph adenoma or from several readily identifiable causes that may interfere with normal dopamine inhibition prolactin (PRL) secretion, such as hypothalamic or pituitary tumors, D2 dopamine receptor antagonist drugs, or hypothyroidism [1]. Nevertheless, despite an extensive clinical, hormonal, and neuroradiological workup, no cause can be found in some patients whose serum PRL concentration may remain elevated for many years [2–7].

In the majority of patients with hyperprolactinemia, monomeric PRL (monoPRL) with a molecular weight of 23 kDa, predominates. Nevertheless, in some patients with hyperprolactinemia, high molecular weight forms of PRL are primarily detected. Such patients are often characterized as having so-called idiopathic hyperprolactinemia. A subset of such patients may harbor microprolactinomas that are left undetected by current imaging techniques. Others may present with elevated macroprolactin (macroPRL) levels as the cause of hyperprolactinemia. Macroprolactinemia is a term applied to the predominance of high molecular mass circulating PRL forms that have been postulated to represent complexes of PRL and anti-PRL immunoglobulins [8–10]. In such cases, recognition of high molecular weight PRL can be achieved by gel filtration chromatography or by a simplified method using polyethylene glycol (PEG) precipitation.

The best recognized symptom of hyperprolactinemia is galactorrhea, but other more subtle symptoms may result from concomitant hypothalamic–pituitary dysfunction including infertility, decreased libido, impotence, and menstrual abnormalities [1]. The clinical significance of macroprolactinemia is controversial. While some investigators have reported on associations with galactorrhea, menstrual irregularities, infertility, and erectile dysfunction [2, 3, 7, 11, 12], conflicting studies have suggested macroprolactinemia to be asymptomatic [13, 14].

The aim of this study was to establish an association between macroprolactinemia and its clinical and radiological findings.

Materials and methods

Study design

This prospective study was undertaken in the Endocrinology Department at Ankara Numune Teaching and Research Hospital with the approval of the local ethics committee.

Of all the patients who presented to the Endocrinology outpatient clinic between 2007 and 2009, those with elevated serum PRL levels were screened, and consenting patients were evaluated for enrollment in the study. A detailed history was obtained for each patient, and the presence of irregular menses, galactorrhea/amenorrhea, erectile dysfunction, headaches, visual changes, and infertility were particularly noted, where relevant. This was followed by a complete physical examination. Pregnant or lactating women, those with primary hypothyroidism, renal or hepatic failure, polycystic ovary syndrome, intercostal nerve stimulation or pituitary stalk injury like trauma or surgery were excluded from the study. Patients with drug-induced hyperprolactinemia were included for evaluation with respect to macroprolactinemia. Eligible participants with hyperprolactinemia were evaluated under four subgroups based on etiology; prolactinoma, drug-related, idiopathic hyperprolactinemia, and macroprolactinemia. Although different causes of hyperprolactinemia may result in varying increases in macroPRL levels, in daily practice cases of macroprolactinemia are grouped under "isolated macroprolactinemia" [7].

Measurement of total prolactin levels

Prior to enrollment, the presence of hyperprolactinemia was confirmed in all patients, for which blood samples were obtained in the morning after an overnight fast. A non-stressed state without prior intercourse or breast stimulation was first ensured.

Baseline serum PRL levels were measured using the Unicel DxI 800 (Access Immunoassay Systems, Beckman Coulter) immunoassay kit. The analytical sensitivity of the assay was 0.25 ng/ml, and current and total coefficients were 1.54 and 4.23%, respectively. Normal values were 2.64–13.12 ng/ml in men, 3.34–26.72 ng/ml in premenopausal women and 2.74–19.64 ng/ml in postmenopausal women.

Assessment of prolactin after PEG precipitation

The PEG precipitation test was performed according to the method proposed by Fahie-Wilson and Soule [15]. Two hundred microliters of a 25% PEG 6000 solution were added, at room temperature, to an equal volume of serum, and the resultant mix was centrifuged for 30 min at $1{,}800 \times g$ and a temperature of 20°C.

Following PEG precipitation, PRL levels in the supernatant were measured without delay using a Unicel DxI 800 immunoanalyser. After correction for dilution, and the values obtained were recorded as PRL "recovered" after

PEG treatment, and the results of the PEG test were provided as a percentage of total or PRL recovery (R%). A R% value of <40% was considered to be indicative of the presence of substantial amounts of macroPRL in the serum (macroprolactinemia), whereas a R% value of ≥40% was considered to be indicative of the absence of macroPRL (monomeric hyperprolactinemia). Participants were stratified into two groups based on R% value (macroPRL and monoPRL groups).

Biochemical assay for other study parameters

Serum levels of creatinine, thyroid stimulating hormone, free thyroxine, adrenocorticotropic hormone, growth hormone; insulin-like growth factor 1, follicle-stimulating hormone, luteinizing hormone, testosterone, and free testosterone were determined using commercial immunoassay kits.

Pituitary imaging

Magnetic resonance imaging (MRI) was performed at 1.5 T, in sagittal and coronal planes with 2.5 mm slice thickness, without an interslice gap. T1-weighted spin-echo images were acquired with a repetition time of 500 ms and echo time of 15 ms, both before and after administration of 5 cc of gadolinium contrast. Based on MRI findings, microadenoma was defined as the presence of a pituitary tumor measuring <10 mm at its greatest diameter and macroadenoma was defined as a tumor measuring 10 mm or more at its greatest diameter.

Patients who presented with visual disturbances and all patients with documented macroadenomas were evaluated by formal visual field examinations and by a designated neurosurgeon. Measurements were obtained in three dimensions [longitudinal (L), width (W), and depth (D)], and tumor volume (V) was calculated using the ellipse formula ($\pi/6 \times L \times D \times W$).

Subjects with incomplete work-up or unconfirmed elevations were excluded from the final analysis.

Statistical analysis

Data analysis was performed by using Statistical Package for Social Sciences (SPSS) version 13.0 software (SPSS Inc., Chicago, IL). Metric discrete variables were given as mean ± standard deviation, and percentages were used for categorical variables. Comparison of categorical variables between groups was performed using the χ^2 test, and in the event of a sample size of <5, Fisher's exact test was used.

Numerical variables were compared using the Mann–Whitney *U* test. A *P* value of <0.05 was considered indicative of statistical significance.

Results

A total of 337 patients with hyperprolactinemia were included in the final analysis, of which 29 were men (8.6%) and 308 were women (91.4%), with a mean age of 33.8 ± 10.8 years (range 16–66). Elevated macroPRL levels were detected in 88 patients (26.1%), 4 of which were male and 84 were female.

After stratification into two groups based on R% values, the mean level of monoPRL was found to be higher in the monoPRL group compared to the macroPRL group (200.1 ± 551.6 vs. 29.5 ± 49.9, $P < 0.001$). The mean ratios of macroPRL in the macroPRL and monoPRL groups were 79.3 ± 12.1 and 24.2 ± 18.0%, respectively ($P < 0.001$). There was no difference between groups with regards to tumor size ($P = 0.066$). The demographic and clinical characteristics of the study population have been summarized in Table 1.

A comparison of clinical presentations did not reveal a significant difference between the macroPRL and monoPRL groups with regards to rates of amenorrhea (12.3 vs. 28.8%, $P = 0.054$), irregular menses (35.8 vs. 54.3%; $P = 0.067$), erectile dysfunction (50.0 vs. 72.0%, $P = 0.469$), infertility (4.9 vs. 10.8% in women, 0 vs. 16.0% in men; $P > 0.05$ for both genders), gynecomastia (25.0 vs. 12.0%; $P = 0.505$), and headaches (9.5 vs. 19.6% for women, 25.0 vs. 16.0% in men, $P > 0.05$ for both genders) (Table 2). Galactorrhea was encountered more frequently in women from the monoPRL group compared to the macroPRL group (39.2 vs. 57.1%; $P = 0.02$). Although there was no difference between groups in terms of rate of asymptomatic males [50% in macroPRL group vs. 28.0% asymptomatic in monoPRL group ($P = 0.312$)], more women in the macroPRL group were asymptomatic compared to those in the monoPRL group (32.1 vs. 10.7%, $P = 0.002$). Table 3 shows a summary of comparisons between groups.

Among all of the patients with hyperprolactinemia, normal findings on pituitary imaging were observed in 77

Table 1 Characteristics of study patients, stratified by type of prolactin

Variable	MonoRPL ($n = 249$)	MacroPRL ($n = 88$)	*P* value
Age (year)	35.0 ± 10.1	30.7 ± 9.8	0.016
Females [no. (%)]	224 (90)	84 (95.5)	0.091
Total prolactin (ng/ml)	125.3 ± 123.9	95.6 ± 47.3	0.158
Monomeric prolactin (ng/ml)	94.6 ± 110.0	17.0 ± 15.6	<0.001
Macroprolactin (%)	30.7 ± 27.5	78.6 ± 45.4	<0.001
Tumor volume (cm^3)	0.47 ± 2.26	0.49 ± 1.33	0.066

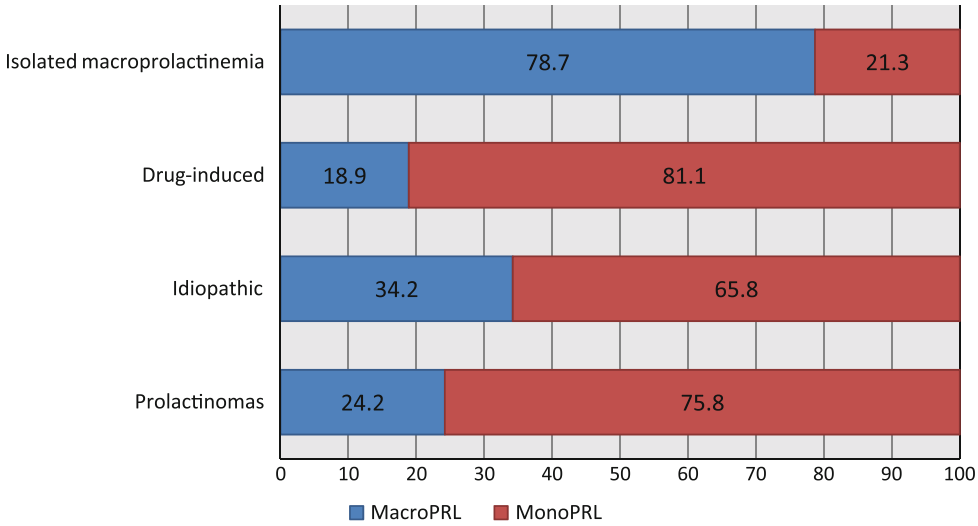

Fig. 1 Frequency of macroprolactinemia according to main diagnostic criteria in patients with elevated prolactin levels

Table 2 Presenting complaints of study population, stratified by gender and dominant type of prolactin

Presenting complaint	Men			Women		
	MonoPRL ($n = 25$)	MacroPRL ($n = 4$)	P value	MonoPRL ($n = 224$)	MacroPRL ($n = 84$)	P value
Erectile dysfunction	18 (72.0)	2 (50.0)	0.469	NA	NA	NA
Infertility[a]	4 (16.0)	0	0.533	16 (10.8)	4 (4.9)	0.341
Headaches	4(16.0)	1 (25.0)	0.604	44 (19.6)	8 (9.5)	0.240
Irregular menses	NA	NA	NA	100 (54.3)	29 (35.8)	0.067
Galactorrhea	0	0	NA	128 (57.1)	33 (39.2)	0.04
Gynecomastia	3 (12.0)	1 (25.0)	0.505	NA	NA	NA
Amenorrhea	NA	NA	NA	53 (28.8)	10 (12.3)	0.054
None	7 (28.0)	2 (50.0)	0.312	24 (10.7)	27 (32.1)	0.002

NA not applicable

[a] Fertility was evaluated in 229 women (148 monoPRL and 81 macroPRL) and irregular menses and amenorrhea were evaluated in 265 women (184 monoPRL and 81 macroPRL) in the reproductive age

patients (22.8%). Abnormal MRI findings were more prevalent in the monoPRL group compared to the macroPRL group [81.1% (202 patients) vs. 65.9% (58 patients); $P = 0.02$]. In the macroPRL group, 48 patients (54.5%) had microadenomas, six patients (6.8%) had macroadenomas and four patients (4.5%) had empty sellas. On the other hand, 161 patients (64.7%) in the monoPRL group had microadenomas compared to 35 patients (14.0%) with macroadenoma, three patients (1.2%) with empty sella and three patients (1.2%) with hypophysitis. Comparison of size of microadenomas between groups revealed that in 28 (58.3%) patients in the macroPRL group, adenomas were smaller than 3 mm, whereas 33 (20.5%) patients in monoPRL group had microadenomas <3 mm in size ($P = 0.088$).

Macroprolactin levels did not differ significantly with underlying etiology, as mean levels obtained for patients with idiopathic hyperPRL, drug-induced hyperPRL and prolactinomas were 34.2 ± 18.5, 18.9 ± 21.0, and 24.2 ± 20.5, respectively ($P = 0.136$) (Fig. 1). Elevated macroPRL levels were encountered more frequently in patients with normal MRI findings compared to those with microadenomas or macroadenomas (50.2 ± 28.7, 35.7 ± 28.1, and 31.8 ± 31.7, respectively; $P = 0.021$).

A break-up of hyperprolactinemic patients with elevated levels of macroPRL revealed that 22 patients (25.0%) had a total PRL level of 30–59 ng/ml, 32 patients (36.4%) with total levels of 60–99 ng/ml, and 23 patients (26.1%) with total levels between 100 and 199 ng/ml. Only 11 patients (12.5%) had total PRL levels in excess of 200 ng/ml. The frequencies of macroprolactinemia based on total PRL levels are displayed in Fig. 2, the highest frequency being observed in patients with PRL levels in the range of 60–99 ng/ml ($P = 0.033$).

A comparison in women based on the presence of macroprolactinemia revealed that a positive clinical finding occurred more commonly in patients with adenoma, although the difference lacked statistically significance (Table 4).

Table 3 Comparison of hormone levels in patients with elevated monomeric prolactin and macroprolactin

Variable	MonoRPL ($n = 249$)	MacroPRL ($n = 88$)	*P* value
TSH (μIU/ml)	1.3 ± 0.7	1.8 ± 0.8	0.072
FT4 (ng/ml)	1.02 ± 0.13	0.95 ± 0.07	0.085
Cortisol (μg/dl)	14.5 ± 6.4	15.9 ± 6.3	0.555
ACTH (pg/ml)	39.2 ± 24.6	32.3 ± 25.0	0.638
GH (*μ*/l)	1.8 ± 3.0	2.3 ± 2.6	0.754
IGF-1 (ng/ml)	243.8 ± 104.8	297.5 ± 71.5	0.091
FSH (mIU/ml)	8.1 ± 10.9	13.0 ± 23.1	0.412
LH (mIU/ml)	4.1 ± 3.1	7.7 ± 5.9	0.030
Estradiol (pg/ml)	69.3 ± 73.2	63.3 ± 62.3	0.826
FT (pg/ml)	4.2 ± 4.9	2.9 ± 1.3	0.601
T (ng/ml)	1.4 ± 1.6	1.0 ± 0.3	0.637

TSH thyroid stimulating hormone; *FT4* free thyroxine; *ACTH* adrenocorticotropic hormone; *GH* growth hormone; *IGF-1* insulin-like growth factor 1; *FSH* follicle-stimulating hormone; *LH* luteinizing hormone; *FT* free testosterone; *T* testosterone

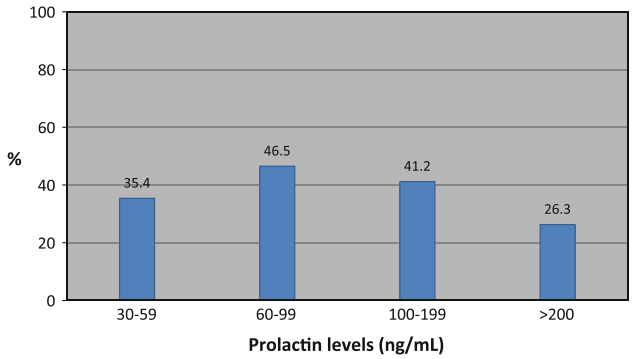

Fig. 2 Frequency of macroprolactinemia based on total prolactin levels in patients with hyperprolactinemia

Table 4 Comparison of clinical and laboratory characteristics of macroprolactinemic patients with and without pituitary adenomas

Clinical findings	With adenoma ($n = 51$)	Without adenoma ($n = 29$)	*P* value
Total prolactin (ng/ml)	97.2 ± 47.6	93.8 ± 46.6	0.838
Monomeric prolactin (ng/ml)	21.7 ± 17.3	18.0 ± 15.7	0.522
Infertility	6 (11.7)	2 (6.9%)	0.708
Irregular menses	10 (19.6)	4 (13.7)	0.301
Galactorrhea	22 (43.1)	9 (31.0)	0.740
Amenorrhea	8 (15.7)	2 (6.9)	0.488
Symptomatic	36 (70.6)	17 (58.6)	0.419

Discussion

In this study, the prevalence of macroprolactinemia was 26.1%. All of the signs and symptoms generally associated with hyperprolactinemia were observed in patients with macroprolactinemia, regardless of gender. Furthermore, elevated macroPRL levels were also observed in association with usual causes of hyperprolactinemia.

Table 5 Comparison of frequency of main clinical findings in women with macroprolactinemia in our study and other major publications

Symptoms	Vallette-Kasic et al. [7] ($n = 96$)	Gibney et al. [19] ($n = 32$)	Present study ($n = 84$)
Infertility	32.0	22.0	4.9
Menstrual disturbances	39.0[a]	59.0[a]	12.3[a]/35.8[b]
Galactorrhea	46.0	22.0	39.2

[a] Oligo/amenorrhea

[b] Irregular menses-amenorrhea

In the human serum, PRL circulates in three forms: monoPRL (molecular weight: 23 kDa), which is the usual form, big PRL (molecular weight 50–60 kDa) and "big big PRL," otherwise known as macroPRL (molecular weight 150–170 kDa) [16, 17]. In the normal population, big PRL accounts for <10% of circulating PRL, whereas macroPRL comprises an even lower proportion (<1%) of total PRL [11].

Prevalence of macroprolactinemia among hyperprolactinemic patients ranges from 10 to 40%, depending on the definition used and the method employed [7, 11, 15, 18, 19]. We established a rate of 26.1%, consistent with previous findings (Table 5).

The clinical significance of macroprolactinemia has been a matter of debate for many years. Some reports have associated it with galactorrhea, menstrual irregularities, infertility, and erectile dysfunction whereas others have suggested that it causes no symptoms [2, 3, 7, 11, 12, 18, 20]. In this study, clinical findings traditionally associated with hyperprolactinemic patients were all observed in those with macroprolactinemia, and these results challenge the traditional view that macroPRL has lower in vivo effectiveness [10, 21].

Menstrual irregularities, and galactorrhea were the most common presenting complaints in women, and erectile dysfunction was the most frequent initial complaint in men from both monoPRL and macroPRL groups. Overall, 67% of the patients with macroprolactinemia were symptomatic. At 46.4%, irregular menses and/or amenorrhea were the most frequently encountered presenting findings in women with macroprolactinemia. Although the frequency of amenorrhea, irregular menses, and infertility seemed to be higher in patients with elevated monoPRL levels, the difference was statistically insignificant. A statistically significant difference was only observed with regards to the

frequency of galactorrhea, which was higher in the monoPRL group compared to the macroPRL group (57.1 vs. 39.2%). Rates of menstrual irregularities and galactorrhea in our macroprolactinemia group are in line with previous studies [7, 19]; however, we encountered a relatively lower prevalence of amenorrhea (Table 5). The low frequency of infertility in our patient group may be explained by the fact that patients with infertility tend to apply directly to fertility clinics, and therefore do not undergo meticulous endocrinological evaluation.

Despite the limited number of subjects for evaluation, erectile dysfunction, and male infertility were encountered significantly more frequently in the monoPRL group compared to the macroPRL group. On the other hand, gynecomastia occurred more commonly in men with macroprolactinemia, albeit the difference between groups bordered on significance.

Abnormal findings on pituitary imaging were detected in 77.2% of patients with hyperprolactinemia, while the prevalence of microadenomas was 62.0%. On the other hand, the frequency of incidental microadenomas in the general population is 10%. Our study results, with regards to radiological imaging, are consistent with those of other studies on patients with hyperprolactinemia. In one such study on hyperprolactinemic patients, the reported prevalence of microadenomas and macroadenomas was 51.3 and 8.1%, respectively [22]. In another study, a pituitary adenoma was detected in 74% of the patients with hyperprolactinemia (55% microadenomas and 19% macroadenomas) [23].

Abnormal MRI findings were more prevalent in patients with elevated monoPRL levels than in patients with macroprolactinemia (81.1 and 65.9%, respectively). We identified pituitary microadenomas in 54.5% of our patients with macroprolactinemia. In another report, abnormal pituitary images were found in 21.1% of patients who had macroprolactinemia and in 75% of patients with monomeric hyperprolactinemia [2]. In a recent study from Turkey, a pituitary adenoma was present in 26.7% of patients with macroprolactinemia [24]. In a study by Valette-Kasic et al. [7], a pituitary pathology was detected in 37.4% of patients with normal chromatography compared to 17.0% of those with macroprolactinemia. However, in this study, the absolute levels macroPRL of all patients with hyperprolactinemia were not taken into consideration, while in our investigation, macroPRL levels and pituitary images were obtained for all patients, which may explain the relatively higher frequency of abnormal MRI findings we observed in association with hyperprolactinemia. We insured that only patients with confirmed elevations of PRL were included in the final analysis, and in those with documented micro/macroadenomas (detected by MRI), further evaluation of pituitary hormones was performed. The highly "select" nature of this study population means that our results cannot be used to reflect the actual frequency of pituitary pathology in patients with macroprolactinemia and monomeric prolactinemia in the general population. However, our study does help to show that patients with pituitary adenomas may also have elevated levels of macroPRL. On the other hand, more patients with normal MRI findings had elevated macroPRL levels compared to those with an abnormal finding. Macroprolactinemia may be associated with other causes of hyperprolactinemia. In our study, we observed that different causes of hyperprolactinemia also resulted in macroprolactinemia, though in varying rates.

Although we established an association between several pituitary pathologies and macroprolactinemia, we could not conduct immunochemical evaluations with the purpose of establishing that pituitary adenomas result in an increased production of high molecular weight PRL. Only a limited number of studies have evaluated the relationship between pituitary adenoma and macroprolactinemia via histological confirmation [8, 25–28].

Typically, macroprolactinemia is not usually suspected in patients with PRL levels over 200 ng/ml [29]. However, in our study, we established elevations in macroPRL regardless of total PRL levels, although such elevations occurred most frequently (46.5%) in patients with total PRL levels between 60 and 99 ng/ml. Only 11 (12.5%) patients with macroprolactinemia had a PRL level >200 ng/ml. Gibney et al. [19] discovered that at 27%, the highest frequency of macroprolactinemia occurred in patients with mildly elevated PRL levels (total PRL ≤700 mU/l).

Conclusion

Currently, routine screening for the presence of macroPRL is not recommended for patients with elevated PRL levels. Clinical Practice Guidelines of the Endocrine Society and Pituitary Society suggest that screening for the presence of macroPRL may be warranted in patients with asymptomatic hyperprolactinemia [18, 20]. In our study, symptomatic elevations in macroPRL levels were detected regardless of the cause of hyperprolactinemia, and we believe that discriminating monomeric and macro-PRL is clinically irrelevant. Macroprolactinemia, however, should not just be considered a biochemical variation, and patients with macroprolactinemia should rather be managed solely based on their symptoms and MRI findings. When evaluating a patient referred for hyperprolactinemia, the presence of a pituitary disorder should be investigated after drug-related elevations have been ruled out, regardless of macroPRL or monoPRL levels, since treatment depends on the presence or absence of symptoms. Mild elevations in PRL levels should also raise a suspicion of a mass lesion pressing on the stalk of the hypophysis.

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