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The Impact on Clinical Practice of Routine Screening for Macroprolactin

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Background: Macroprolactin has reduced bioactivity *in vivo* and accumulates in the sera of some subjects, resulting in pseudo-hyperprolactinemia and consequent misdiagnosis.

Methods: We have audited our experience of routine screening for macroprolactin using polyethylene glycol (PEG) precipitation over a 5-yr period in a single center.

Results: Application of a reference range for monomeric prolactin (the residual prolactin present in macroprolactin-depleted serum) for normal individuals revealed that 453 of 2089 hyperprolactinemic samples (22%) identified by Delfia immunoassay were explained entirely by macroprolactin. The percentage of hyperprolactinemic samples explained by macroprolactinemia was similar across all levels of total prolactin (18, 21, 19, and 17% of samples from 700-1000, 1000–2000, 2000–3000, and greater than 3000 mU/liter, respectively). Application of an absolute prolactin threshold after polyethylene glycol treatment of sera, rather than the traditional method, *i.e.* less than 40% recovery, minimizes the opportunity for misclassification of patients in whom macroprolactin accounted for more than 60% of prolactin and the residual bioactive prolactin was present in excess. Macroprolactinemic patients could not be differentiated from true hyperprolactinemic patients on the basis of clinical features alone. Although oligomenorrhea/amenorrhea and galactorrhea were more common in patients with true hyperprolactinemia ($P < 0.05$), they were also frequently present in macroprolactinemic patients. Plasma levels of estradiol and LH and the LH/FSH ratio were significantly greater in macroprolactinemic compared with true hyperprolactinemic subjects ($P < 0.05$). Reduced use of imaging and dopamine agonist treatment resulted in a net cost savings, offsetting the additional cost associated with the introduction of screening.

Conclusion: Routine screening of all hyperprolactinemic sera for macroprolactin is recommended. **(*J Clin Endocrinol Metab* 90: 3927–3932, 2005)**

IN MOST INDIVIDUALS, prolactin (PRL) circulates predominantly as a 23-kDa monomer, with trace amounts of a 60-kDa species and a high-molecular-weight form termed big-big PRL identified on gel filtration chromatography (1–3). Characterization of big-big PRL has revealed that, in the vast majority of cases, it consists of a complex of PRL and an anti-PRL IgG autoantibody, commonly referred to as macroprolactin (4, 5). Less commonly, other forms of macroprolactin have been described, often in patients with prolactinomas. Such forms are heterogeneous, often composed of either covalent or noncovalent polymers of monomeric PRL, with molecular mass ranging up to approximately 500 kDa (6–12).

Although macroprolactin has been shown to exhibit varying degrees of biological activity *in vitro* (5, 13–16), because of its high molecular mass the complex is confined to the vascular system *in vivo* and hence is bio-unavailable (14, 17). Delayed metabolic clearance (7, 15) together with detection by most automated PRL immunoassay systems (18–20) leads to pseudo-hyperprolactinemia in patients harboring this form of complexed PRL. Presenting symptoms in patients with hyperprolactinemia due to macroprolactin vary. In some instances, the condition is identified serendipitously in the absence of symptoms (21). For many patients, the classic symptoms of the hyperprolactinaemic syndrome are absent, whereas other patients present with atypical features (13, 14, 16, 22–24) or varying degrees of infertility, menstrual disorders, and/or galactorrhea (14, 25–31). These findings are not surprising in that the symptoms of hyperprolactinemia that prompt measurement of PRL are nonspecific and may occur coincidentally in patients who present with hyperprolactinemia due to macroprolactin.

The high prevalence of pituitary lesions identified incidentally by scanning and at autopsy suggest that a similar coincidental association is likely to occur with macroprolactinemia. As a result, there have been many reports of inappropriate investigation and treatment of subjects in whom elevated levels of PRL were later found to be explained by macroprolactin (30, 32–36). The frequency of abnormal imaging in macroprolactinemic patients (8–20%) (26–28, 30, 31) is similar to that found in unselected subjects undergoing pituitary imaging for reasons other than suspected pituitary disease (6–20%) or to pituitary abnormalities found at autopsy (10–24%), as reported by Molitch and Russell (37). Thus, the frequency of abnormal pituitary images in subjects with macroprolactinemia is not higher than expected for the general population. Failure to appreciate this coincidental association has led to at least two reported instances of unnecessary and unhelpful pituitary exploration (26, 36). In contrast, recognition that hyperprolactinemia was entirely explained by macroprolactin prompted conservative management of patients with abnormal pituitary imaging (38, 39).

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Abbreviations: CT, Computed tomography; DA, dopamine agonist; MRI, magnetic resonance imaging; PEG, polyethylene glycol; PRL, prolactin.

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Macroprolactinemia, whereas hyperprolactinemia can be entirely accounted for by macroprolactin, is conservatively estimated to account for 10% of hyperprolactinemia in the United States and in the United Kingdom (18, 30). Although effective screening tests are available to detect macroprolactin, these are often not routinely used. Moreover, testing for macroprolactin in the past has been reserved for those subjects with elevated serum PRL levels but clinical features or a response to treatment not typical of true hyperprolactinemia. Validation of the polyethylene glycol (PEG) precipitation technique (40, 41) has enabled large-scale screening for macroprolactin in hyperprolactinemic subjects. Such screening has revealed that macroprolactinemia also commonly occurs in subjects with apparently typical features of hyperprolactinemia (30).

In our center, we have routinely screened all hyperprolactinemic samples for macroprolactin using PEG precipitation since 1998. When PRL levels after PEG precipitation fall within a reference range derived from similarly treated normal sera, this is considered a normal result (30), and it is recommended that an explanation other than hyperprolactinemia be sought for the patient's clinical features. The alternative method of defining macroprolactinemia is recovery of less than 40% of PRL in serum after PEG precipitation (25, 26). This latter approach does not completely exclude simultaneous occurrence of an absolute elevation of monomeric PRL and has resulted in misclassification in the past (42). Such patients, while having elevated levels of serum macroprolactin, also have elevated levels of monomeric PRL. In such cases, the presence of excess bioactive monomeric PRL is clearly of overriding clinical concern.

The aim of this study was to review the clinical setting in which macroprolactinemia was identified and to assess the impact of routine screening for macroprolactin, using PEG precipitation, over a 5-yr period in a single center on patient management and service costs. We have also examined the occurrence of true hyperprolactinemia, *i.e.* elevated absolute levels of residual PRL in sera after PEG precipitation, in which residual PRL constituted less than 40% of total PRL.

Subjects and Methods

Since 1998, all samples with a PRL above the upper limit of the normal reference range (female, 500 mU/liter; male, 290 mU/liter), analyzed at the Endocrine Laboratory of St. Vincent's University Hospital, have been submitted to PEG precipitation. Results are expressed as total PRL and bioactive monomeric PRL, *i.e.* PRL remaining after PEG treatment. When the value of PRL in PEG-treated sera fell to within an established normal reference range (female, <403 mU/liter; male, <230 mU/liter), it was considered and reported as a normal result (30). PRL levels in normal adult sera after PEG treatment ranged from 70–403 mU/liter in females (n = 110) and 68–230 mU/liter in males (n = 32). For the purposes of the current study, we have evaluated all hyperprolactinemic samples identified between January 1999 and December 2003. Evaluation of management of patients, before the introduction of routine screening for macroprolactin, *i.e.* before January 1999 and subsequently documented retrospectively to have either true hyperprolactinemia or macroprolactinemia, was confined to patients with total PRL greater than 700 mU/liter. True hyperprolactinemia is defined as the finding of PRL levels in excess of 403 mU/liter in women or in excess of 230 mU/liter in men after treatment of hyperprolactinemic sera with PEG.

Study subjects

Case notes of all patients with elevated PRL (female, 500 mU/liter; male, 290 mU/liter) who attended a general endocrinology outpatient service in a university-affiliated teaching hospital and tertiary referral center during the 5 yr of the study were reviewed. From these records, it was possible to obtain information on symptoms and signs, imaging investigations, diagnoses, and treatment used. In addition to PRL levels, plasma levels of FSH, LH, and estradiol were available in all female subjects. It is our practice to measure reproductive hormone levels in the follicular phase in menstruating women. Comparisons were made between patients who continued to have elevated levels of PRL after PEG precipitation (true hyperprolactinemic) and those in whom PRL levels normalized after PEG treatment (macroprolactinemic). Analysis of hormonal data were confined to women who were not receiving medications likely to interfere with results and to avoid the potentially confounding effect of menopause, to women aged 45 yr or less. Approval for this study was obtained from the Research Ethics Committee of St. Vincent's University Hospital.

Assay methodology

Serum PRL, estradiol, FSH, and LH levels were measured using commercially available fluoroimmunoassays (Auto Delfia; PerkinElmer Wallac, Turku, Finland). To estimate the amount of bioactive monomeric PRL present, specimens were assayed for PRL after treatment with PEG 8000 as outlined previously (30). Briefly, 250 μl serum, mixed with an equal volume of 25% (wt/vol) PEG in PBS (pH 7.4), was incubated for 10 min at room temperature. After clarification of the suspension by centrifugation, the monomeric PRL level in the supernatant was quantified by Delfia. The reproducibility of the PEG precipitation procedure was monitored by inclusion of control sera in each assay. At PRL levels of 148 and 836 mU/liter after PEG treatment, the interassay coefficient of variation values were 6.4% (n = 63) and 5.2% (n = 46), respectively. Conversion of PRL values from milliunits per liter to micrograms per liter is achieved by dividing by 36. Conversion of estradiol levels from picomoles per liter to nanograms per milliliter is achieved by dividing by 3.67.

Statistical analysis

Statistical analysis of clinical characteristics was performed using the χ^2 test for categorical variables and Student's unpaired t test for continuous variables. Results are expressed as median (range), and statistical significance was set at an α level of 0.05. When multiple comparisons were made, Bonferroni's correction was introduced.

Results

Frequency of macroprolactinemia

Plasma levels of PRL were above the normal range in 2089 sera or 21% of samples analyzed. Of these samples, 1752 were derived from women, and 337 were from men. Total PRL levels more than 700 mU/liter were identified in 1305 (62% of hyperprolactinemic) samples.

Application of a reference range for monomeric PRL, *i.e.* residual PRL in serum after PEG precipitation, derived from normal individuals revealed that 453 of the hyperprolactinemic samples (22%) were explained by macroprolactin, *i.e.* the monomeric PRL levels fell to less than 403 mU/liter in women and to less than 230 mU/liter in samples from men after treatment of sera with PEG. A lower percentage of male hyperprolactinemic samples (12%) were explained by macroprolactin compared with female hyperprolactinemic samples (24%; $P < 0.05$).

The percentage of hyperprolactinemic samples explained by macroprolactin varied with the total PRL level (Fig. 1). A higher percentage of macroprolactinemia (27%) was found in subjects with mild hyperprolactinemia (total PRL ≤700 mU/

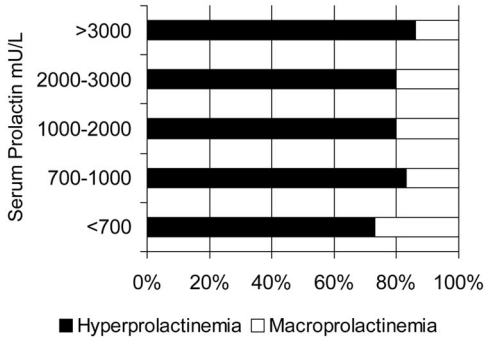

FIG. 1. Percentage of 2089 hyperprolactinemic samples explained by true hyperprolactinemia (*black bars*) or macroprolactinemia (*white bars*) expressed in relation to total serum PRL.

liter; $P < 0.05$). However, the percentage of clinically significant hyperprolactinemic samples explained by macroprolactin was similar across all levels of total PRL (18, 21, 19, and 17% of samples from 700-1000, 1000–2000, 2000–3000, and >3000 mU/liter, respectively) (Fig. 1).

Comparison of presenting clinical features in true hyperprolactinemic and macroprolactinemic female subjects

Table 1 summarizes clinical data in female patients identified as having either true hyperprolactinemia or macroprolactinemia when confining the evaluation to patients with PRL levels more than 700 mU/liter. Sixty of these patients were attending the Endocrinology Outpatient Clinic before and 72 were referred after commencement of routine screening for macroprolactin. Total PRL levels were similar in patients with true hyperprolactinemia or macroprolactinemia. After PEG treatment, PRL fell from 1145 (517–3390) to 240 (99–384) mU/liter in macroprolactinemic patients and from 1315 (514–6775) to 992 (393–5776) mU/liter in true hyperprolactinemic patients (Table 1). In both groups, oligomenorrhea was the most frequent symptom at presentation, whereas galactorrhea, headache, and infertility occurred less frequently (Table 1). Although galactorrhea and oligomenorrhea were more common in patients with true hyperprolactinemia ($P < 0.05$), there was no difference in frequency of headache or infertility between the two groups (Table 1).

TABLE 1. Clinical and laboratory data in true hyperprolactinemic and macroprolactinemic female subjects

Characteristics	Hyperprolactinemia (n = 100)	Macroprolactinemia (n = 32)
Age (yr)	35 (19–69)	29 (18–59)
Total PRL (mU/liter)	1315 (514–6775)	1145 (517–3390)
PRL after PEG precipitation (mU/liter)	992 (393–5776)	240 (99–384)[a]
Clinical features[b]		
Oligomenorrhea or amenorrhea	73%	59%[a]
Galactorrhea	54%	22%[a]
Infertility	7%	22%
Headache	7%	5%

Data are median (range). To convert PRL values from milliunits per liter to micrograms per liter, divide by 36.

[a] $P < 0.05$ *vs.* true hyperprolactinemic subjects.

[b] Premenopausal subjects only with PRL levels more than 700 mU/liter.

Management of true hyperprolactinemic and macroprolactinemic female patients

Patients attending before the introduction of routine screening for macroprolactin. Of the 60 patients attending the Endocrinology Outpatient Clinic before the introduction of routine screening for macroprolactin, computed tomography (CT) or magnetic resonance imaging (MRI) scanning was performed in 11 of 15 patients (73%) who were subsequently found to have macroprolactinemia (Table 2) and in 37 of 45 patients (82%) confirmed to have true hyperprolactinemia. Although the frequency of scanning did not differ between the groups, abnormalities were predominantly found in the hyperprolactinemic group (15 *vs.* 2). Of the 37 scans performed in true hyperprolactinemic subjects, 22 were normal, nine revealed changes consistent with a microadenoma, and six revealed a macroadenoma. Changes consistent with a microadenoma were seen in two subjects with macroprolactinemia, but no macroadenoma was seen in this group (Table 2).

Dopamine agonist (DA) treatment was prescribed in 13 of 15 patients (87%) who were subsequently found to have macroprolactinemia and in 37 of 45 patients (82%) confirmed to have true hyperprolactinemia. Treatment with DA resulted in a decrease in serum PRL from 1726 ± 279 to 389 ± 98 mU/liter in the macroprolactinemic group and from 2393 ± 235 to 309 ± 55 mU/liter (mean ± SD) in the true hyperprolactinemic group. Symptomatic improvement was reported by 15 of 19 women with true hyperprolactinemia and galactorrhea who were treated with DA. Of the four women with macroprolactinemia and galactorrhea who were treated with DA, all noted symptomatic improvement. Menses increased in frequency in 17 of 23 women with true hyperprolactinemia and oligomenorrhea or amenorrhea who were treated, whereas an additional two became pregnant. In contrast, of the eight women with macroprolactinemia and oligomenorrhea or amenorrhea treated with DA, increased frequency of menses occurred in one woman only.

Table 2 details presenting features, laboratory, and radiological investigations in 15 female patients diagnosed as having hyperprolactinemia before the introduction of screening for macroprolactin but in whom a subsequent diagnosis of macroprolactinemia was made. As a consequence, alternative diagnoses were made, DA treatment was stopped, and, in some cases, more appropriate treatment was instituted. For example, one patient with infertility secondary to polycystic ovary syndrome was successfully treated with clomiphene, and another patient with tubal damage was successfully treated with surgery.

Patients diagnosed after the introduction of routine screening for macroprolactin. Pituitary imaging was performed in 33 of 55 newly diagnosed patients with true hyperprolactinemia, and DA treatment was commenced in 25. No subjects with macroprolactinemia underwent pituitary imaging, and none were treated with DA. All macroprolactinemic patients were reassured that hyperprolactinemia was unlikely to underlie their clinical presentation.

Hormonal data in female subjects

Plasma levels of estradiol were significantly greater in macroprolactinemic compared with true hyperprolactinemic

TABLE 2. Clinical characteristics of 15 patients, with total PRL levels more than 700 mU/liter, retrospectively diagnosed as having macroprolactinemia; subsequent diagnosis and management

Patient no.	Age (yr)	Serum PRL (mU/liter)		O/A	Symptoms			Pituitary imaging	Revised diagnosis
		Not PEG-treated	PEG-treated		G	I	H		
1	15	1760	230	Y	N	N	N	NOR	Cyclical mastalgia
2	27	1206	344	Y	Y	N	N	MA	OCP-related galactorrhea
3	26	2240	192	Y	N	N	Y	NOR	PCOS
4	20	1940	378	Y	Y	Y	N	MA	PCOS
5	33	1288	214	Y	N	N	N	NOR	DUB
6	29	1360	171	Y	N	N	Y	ND	Low body weight
7	22	1310	236	Y	N	N	N	NOR	Bulimia nervosa
8	21	819	302	N	Y	N	N	NOR	Idiopathic galactorrhea
9	38	1590	232	N	N	Y	N	NOR	Paratubular cyst
10	55	1530	224	Y	N	N	N	NOR	Menopause
11	38	3390	248	N	Y	N	N	NOR	Idiopathic galactorrhea
12	40	883	337	Y	N	N	N	ND	Menopause
13	28	1037	24	Y	N	N	N	NOR	PCOS
14	32	4021	142	N	N	N	N	NOR	Unexplained miscarriage
15	33	891	194	Y	Y	N	Y	NOR	Infertility related to SLE

G, Galactorrhea; O/A, oligomenorrhea/amenorrhea; I, infertility; MA, microadenoma; ND, not done; PCOS, polycystic ovary syndrome; H, hirsutism; OCP, oral contraceptive pill; DUB, dysfunctional uterine bleeding; SLE, systemic lupus erythematosis; Y, yes; N, no; NOR, normal.

subjects (Fig. 2). There was, however, an obvious overlap between the groups. Plasma levels of LH [6.4 (2.8–43.6) *vs.* 5.6 (0.5–19.6) U/liter; $P < 0.002$] and the LH to FSH ratio [1.5 (0.5–5.4) *vs.* 1.2 (0.1–6.2); $P < 0.02$] were also significantly greater in macroprolactinemic subjects. Plasma levels of FSH did not differ between the groups [5.2 (1.9–8.7) *vs.* 5.1 (1.1–12.4) U/liter].

Comparison of different approaches to the identification of patients with macroprolactinemia

Comparisons were also made between two methods for categorising subjects as having macroprolactinemia or true hyperprolactinemia, *i.e.* the normative data approach *vs.* the percentage recovery approach. In the former case, for a patient to be classified as macroprolactinemic, the residual PRL level must fall to less than that observed after treatment of normal sera with PEG, *i.e.* less than 403 mU/liter in females and less than 230 mU/liter in males. In contrast, use of the more traditional approach of a percentage cutoff requires that serum PRL falls to less than 40% after PEG treatment for a patient to be classified as macroprolactinemic. Of the 1305 subjects with clinically significant hyperprolactinemia, 230 subjects were identified as having macroprolactinemia, and 1036 were identified as having true hyperprolactinemia using either the normative data or the percentage macroprolactin approach (Table 3). Twenty-eight (2%) subjects were considered to be hyperprolactinemic using the normative data reference range but macroprolactinemic using the 40% threshold. PRL levels after PEG precipitation in these individuals ranged from 412-3060 mU/liter. Eleven subjects (1%) were considered to be macroprolactinemic using the normative data reference range but hyperprolactinemic using the 40% threshold. PRL levels after PEG precipitation in these individuals ranged from 300–376 mU/liter.

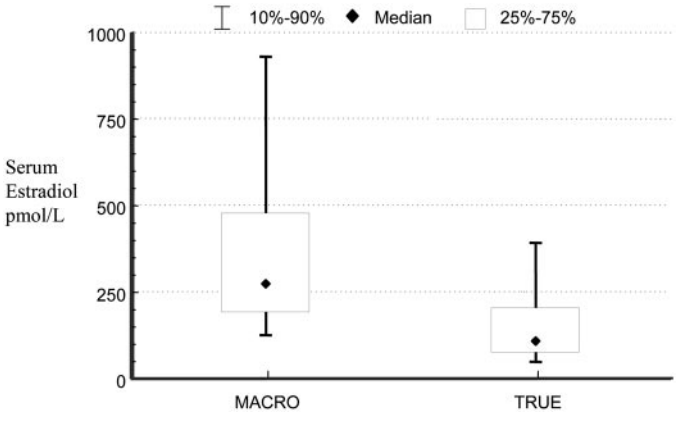

FIG. 2. Serum estradiol levels in women with macroprolactinemia (MACRO) or true hyperprolactinemia (TRUE).

Cost effectiveness

In our cohort of patients in whom PRL was measured, 21% proved to be hyperprolactinemic. In screening for macroprolactin, this 21% had PRL remeasured after PEG precipitation, which incurred an additional cost of 30%. This resulted in an overall increase in the cost of measuring PRL, including screening for macroprolactin in hyperprolactinemic sera, of 27%. Screening for macroprolactin resulted in a 15% decrease in costs associated with CT/MRI imaging by avoiding their use in approximately 70% of those with unidentified macroprolactinemia, *i.e.* 21% of all hyperprolactinemic subjects. This figure is based on the finding in this study that 73% of unidentified macroprolactinemic subjects underwent CT or MRI. Similarly, screening for macroprolactin resulted in a 17% decrease in expenditure on treatment associated with the prescription of DA for 80% of unidentified macroprolactinemic subjects. This figure is based on the finding that

TABLE 3. Comparison of methods for categorization of subjects as either true hyperprolactinemic (True) or macroprolactinemic (Macro)

Percent recovery	Normative data	
	True	Macro
True (>40%)	1036	11
Macro (<40%)	28	230

80% of patients retrospectively identified with macroprolactin accounting entirely for their hyperprolactinemia were treated with DA. In our institution, the overall cost savings achieved by routine screening for macroprolactin was greater than the additional cost of screening.

Discussion

This retrospective study demonstrated that, using the PEG precipitation technique, 22% of all hyperprolactinemic samples identified by our laboratory over a 5-yr period were explained by macroprolactin. When marginal hyperprolactinemia—PRL between 500 and 700 mU/liter—was excluded, the percentage of hyperprolactinemic samples explained by macroprolactin was consistent across all levels of total PRL. No clinical features could reliably differentiate macroprolactinemic from true hyperprolactinemic patients, and, although LH and estradiol levels were significantly higher in macroprolactinemic patients, there was an obvious overlap between the two groups. Reduced use of pituitary imaging and DA treatment resulted in a net cost savings attributable to routine screening for macroprolactin.

The proportion of hyperprolactinemic sera explicable by macroprolactinemia is assay dependent and, in most studies, has been reported as between 15 and 35% (14, 25–27, 29, 30). One study reported a prevalence of 46% (28), but it is likely that this particularly high incidence reflected selection bias because of the specialized nature of the study center, which received samples sent from other laboratories when the possible diagnosis of macroprolactinemia was raised. In the current study, the number of samples explained by macroprolactinemia was similar whether it was determined by comparison with reference data derived form normal subjects or by percentage recovery of PRL after PEG precipitation. A number of subjects (2% of the total) were identified who would have been categorised as macroprolactinemic using percentage recovery of PRL, *i.e.* less than 40%, but in whom residual levels of PRL remained significantly elevated (up to 3060 mU/liter) after PEG precipitation. In these subjects, it is likely that elevated PRL levels contributed to the presenting clinical features, although they would have been considered macroprolactinemic using traditional criteria. Conversely, a smaller proportion of subjects (1%) were identified as having true hyperprolactinemia using percentage recovery but macroprolactinemic when compared with normative data. PRL levels in these individuals after PEG precipitation ranged from 300–376 mU/liter. The use of absolute reference values to identify patients with normal PRL levels after PEG treatment minimizes the opportunity for misclassifying patients inherent in the use of percentage recovery when screening sera for macroprolactinemia. In addition, although PEG has proved to be a particularly useful reagent in distinguishing macroprolactinemia from true hyperprolactinemia, it is not a specific reagent, and, as with any biochemical test, the result obtained should always be interpreted in the context of the clinical setting.

We confirmed our previous observation that macroprolactinemic subjects could not be differentiated from true hyperprolactinemic subjects other than by measurement of macroprolactin (30). Although galactorrhea and oligomenorrhea occurred less commonly in patients with macroprolactinemia, at least one of these symptoms was present in most macroprolactinemic patients, reflecting the original reason why the test was ordered. Plasma levels of LH and estradiol were greater in macroprolactinemic compared with true hyperprolactinemic patients, consistent with a reduced ability of macroprolactin to suppress the hypothalamic-pituitary-ovarian axis, but there was a significant overlap between the two groups. Thus, although an unexpectedly normal estradiol level in a patient with clinically significant hyperprolactinemia might suggest macroprolactinemia, normal estradiol levels also occur in the setting of true hyperprolactinemia, and, conversely, estradiol levels are sometimes suppressed in macroprolactinemic subjects.

Identification of macroprolactinemia altered patient management. Most macroprolactinemic patients who had been attending the Endocrinology Outpatient Clinic before routine screening for macroprolactin had undergone pituitary imaging and were treated with dopamine agonists. These findings are consistent with previous reports of macroprolactinemic patients who had undergone treatment for hyperprolactinemia, including trans-sphenoidal exploration or adenomectomy (36, 42), before the realization that they had macroprolactinemia. Although, there is an additional cost associated with routine screening for macroprolactin, substantial savings can be achieved through diminished requests for imaging procedures and DA prescription, approximately 15–17%, resulting in a net cost benefit. The extent of such benefit will be related to the institutional unit cost. Furthermore, screening for macroprolactin prevents misdiagnosis of hyperprolactinemia, thereby affording the opportunity to make a correct diagnosis for the patient's clinical condition.

In summary, these data show that macroprolactinemia is a common cause of elevated PRL levels, which can give rise to inappropriate investigation and treatment and can delay diagnosis. Routine screening for macroprolactin in hyperprolactinemic samples is cost-effective and can alter management in up to 20% of hyperprolactinemic patients.

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