Frequent Misdiagnosis and Mismanagement of Hyperprolactinemic Patients before the Introduction of Macroprolactin Screening: Application of a New Strict Laboratory Definition of Macroprolactinemia

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Background: Macroprolactin (big big prolactin) has reduced bioactivity and is measured by immunoassays for prolactin when it accumulates in the plasma of some individuals. We applied normative data for serum prolactin after treatment of sera to remove macroprolactin to elucidate the contribution of macroprolactin to misleading diagnoses, inappropriate investigations, and unnecessary treatment.

Methods: We reviewed records of women attending a tertiary referral center who had prolactin >1000 mIU/L. Application of a reference interval to polyethylene glycol (PEG)-treated hyperprolactinemic sera identified 21 patients in whom hyperprolactinemia was accounted for entirely by the presence of macroprolactin. Presenting clinical features, diagnoses, and treatment were compared in these patients and 42 age-matched true hyperprolactinemic patients.

Results: Prolactin concentrations in sera of 110 healthy individuals ranged from 78 to 564 mIU/L. The range of values for the sera after PEG treatment was 70–403 mIU/L. For macroprolactinemic samples, PEG treatment decreased mean (SD) prolactin from 1524 (202) mIU/L to 202 (27) mIU/L but decreased it only from 2096 (233) mIU/L to 1705 (190) mIU/L in true hyperprolactinemic patients (*P* <0.01 between groups). Oligomenorrhea or amenorrhea and galactorrhea were the most common

clinical features in both groups, although they occurred more frequently in true hyperprolactinemic patients (*P* <0.05). Serum estradiol and luteinizing hormone concentrations were significantly higher in participants with macroprolactinemia than in those with true hyperprolactinemia (*P* <0.05). Among participants with retrospectively identified macroprolactinemia, pituitary imaging was performed in 93% and treatment with dopamine agonist was prescribed in 87%.

Conclusions: Macroprolactin is a significant cause of misdiagnosis, unnecessary investigation, and inappropriate treatment. The use of an appropriate reference interval for the PEG immunoprecipitation procedure may be of particular importance in those patients who have an excess of both macroprolactin and monomeric prolactin.

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Hyperprolactinemia is a common cause of galactorrhea, amenorrhea, and infertility in women (*1*). The diagnosis depends on the measurement of circulating prolactin in the appropriate clinical setting. Prolactin circulates in a variety of forms. In normal sera, monomeric prolactin with a molecular mass of 23 kDa accounts for 85–95% of the prolactin present and a 50-kDa species makes up <10%. Big big prolactin, or macroprolactin, a prolactin-IgG complex with a molecular mass of ~150 kDa according to reports, accounts for a small but variable percentage of total prolactin (*2, 3*). Whereas monomeric prolactin is bioactive, macroprolactin is considered biologically inactive, although it retains immunoreactivity (*4–7*). We and others have reported variable detection of macroprolactin by prolactin immunoassays (*8–10*). In some individuals, most of the prolactin may be in the macro-

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prolactin form, leading to "pseudo-hyperprolactinemia" because the biologically inactive prolactin-IgG complex is cleared more slowly than monomeric prolactin (6, 11). Macroprolactin alone can account for up to 26% of all reported cases of hyperprolactinemia depending on the immunoassay used (8, 12–15).

True hyperprolactinemia caused by biologically active prolactin is associated with the suppression of gonadotropin secretion and gonadal activity (16). Individuals found to have macroprolactinemia have been reported to have nonpathologic gonadotropin and gonadal activities (17, 18). The symptoms of hyperprolactinemia, however, are relatively common and nonspecific and, therefore, are likely to occur coincidentally in some patients with macroprolactinemia, as has been reported (12, 14, 19). The high concentrations of macroprolactin detected by commercial immunoassays, together with a failure of laboratories to systematically screen all hyperprolactinemic sera for the presence of macroprolactin, has led to the misdiagnosis of patients and unnecessary medical and surgical intervention (12, 20–22). The need to differentiate between the apparent benign clinical condition of macroprolactinemia, in which hyperprolactinemia is entirely explained by the presence of macroprolactin, and true hyperprolactinemia, which requires therapy, is emerging as a concept.

This study was undertaken to determine the contribution that macroprolactinemia makes to the finding of hyperprolactinemia in routine clinical practice. Conventionally, the diagnosis of macroprolactinemia has been based on the finding that more than 30–60% of prolactin was in the macroprolactin form as indicated by gel-filtration chromatography (12, 15, 23) or that <30% (23) or 40% (12, 15) was recovered after treatment of the serum with polyethylene glycol (PEG).[4] This convention does not acknowledge that, although macroprolactin could account for more than 60% of total prolactin, free prolactin, i.e., prolactin minus macroprolactin, could still be present in biologically significant excess. Thus, patients have been reported to have macroprolactinemia who also had monomeric prolactin concentrations >2000 mIU/L (24). In the present study, a more demanding criterion for the diagnosis of macroprolactinemia has been adopted. The retrospective section of this study, furthermore, allowed assessment of how hyperprolactinemic patients, not then known to have macroprolactinemia, were managed in the past and, by extension, how macroprolactinemic patients are currently being managed when routine assessment of hyperprolactinemic serum does not examine for the presence of macroprolactin.

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[4] Nonstandard abbreviations: PEG, polyethylene glycol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; CT, computed tomography; MRI, magnetic resonance imaging; and DA, dopamine agonist.

Patients and Methods

STUDY PARTICIPANTS

We reviewed case notes of female patients with prolactin >1000 mIU/L attending a tertiary referral center. From these records, we obtained information on symptoms and signs, imaging investigations, diagnoses, and treatment used. Prolactin was measured in all participants at the time of presentation. Macroprolactin was measured in archived sera stored at −20 °C; the macroprolactin had been obtained from individuals who attended before routine screening for macroprolactin or was in the sera obtained at the time of presentation from individuals who attended after the introduction of routine screening. To establish an appropriate reference interval for prolactin in PEG-treated sera, we collected blood from 110 healthy females of reproductive age. For a diagnosis of macroprolactinemia in this study, we needed to use PEG treatment to correct hyperprolactinemia to concentrations obtained in normoprolactinemic sera after PEG treatment.

We identified 21 patients in whom prolactin concentrations fell within the reference interval after PEG precipitation and who were classified as macroprolactinemic. Of these, 15 were identified by retrospective analysis of 79 archived hyperprolactinemic sera (>1000 mIU/L). The remaining 6 patients were identified from 22 patients after the introduction of macroprolactin screening. For each patient with macroprolactinemia, two age-matched true hyperprolactinemic control patients were identified in whom serum prolactin concentrations remained above the reference interval after PEG precipitation. In all cases, clinical details were documented before knowledge of macroprolactin status.

Approval for this study was obtained from the Research Ethics Committee, St. Vincent's University Hospital.

ASSAY METHODOLOGY

Serum prolactin, estradiol, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were measured by the use of commercially available fluoroimmunoassays (Auto Delfia). To estimate the concentration of macroprolactin present, specimens were assayed for prolactin after treatment with PEG 8000 (Sigma P-2139) (15). Briefly, 250 μL of serum, mixed with an equal volume of PEG, 250 g/L in phosphate-buffered saline (137 mmol/L sodium chloride, 10 mmol/L sodium phosphate) at pH 7.4, was incubated for 10 min at room temperature. The suspension was clarified by centrifugation at 1800g for 30 min, and the supernatant was subjected to prolactin analysis. The difference between the prolactin concentrations in the untreated and PEG-treated sera provided a measure of the macroprolactin concentration. (To convert prolactin mIU/L to μg/L, we divide by 36.)

GEL-FILTRATION CHROMATOGRAPHY

Normal sera (0.75 mL) were subjected to gel-filtration chromatography over Sephacryl S-200 (60 cm × 1.5 cm) in

phosphate-buffered saline, pH 7.4, with an AKTA protein purification system (Pharmacia Biotech) at 0.75 mL/min. Eluted protein was quantified by its absorbance at 280 nm. Prolactin concentrations in the fractions (2 mL) were determined by the Delfia immunoassay, with the monomeric prolactin and macroprolactin values derived from the relative areas under the peaks. The column was calibrated with proteins of known molecular mass obtained from Sigma: human IgG (150 kDa); bovine serum albumin (66 kDa), and bovine erythrocyte carbonic anhydrase (29 kDa). In addition, sera containing predominantly macroprolactin or monomeric prolactin, as characterized previously (8), were used for reference purposes.

STATISTICAL ANALYSIS

Comparison of clinical and biochemical characteristics between true hyperprolactinemic and macroprolactinemic individuals was performed by the χ^2 test for categorical variables and the Student unpaired t-test for continuous variables. Comparison of change from baseline between the groups was made by an analysis of covariance. Results are expressed as mean (SE), and statistical significance was set at an α level of 0.05. The reference interval represents the absolute prolactin range obtained for the 110 sera from healthy women, lowest value to highest value.

Results

REFERENCE INTERVAL FOR SERUM PROLACTIN AFTER TREATMENT WITH PEG

Sera from 110 healthy female participants were analyzed for prolactin before and after treatment with PEG. Prolactin in untreated sera ranged from 78 to 564 mIU/L with a mean (SD) of 249 (107) mIU/L. Treatment of the 110 samples with PEG and reanalysis produced a decrease in prolactin values in all of the sera. Prolactin in PEG-treated sera (interval) was 70–403 mIU/L with a mean (SD) of 197 (80) mIU/L. Posttreatment values were 56–95% of the initial values but were 93–98% (mean = 96%) for the Delfia prolactin calibrator (1489 mIU/L; n = 10).

The reproducibility of the PEG precipitation procedure was evaluated for sera with different concentrations of monomeric prolactin and macroprolactin. For a sample with a total prolactin of 297 mIU/L and a corresponding prolactin of 128 mIU/L after treatment with PEG, the interassay CV for the PEG-treated sample was 5.3% (n = 43); with a total prolactin of 627 mIU/L and a prolactin after treatment with PEG of 336 mIU/L, the CV was 5.6% (n = 34); with a total prolactin of 1229 mIU/L and a prolactin after PEG treatment of 1090mIU/L, the CV was 4.9% (n = 22).

PROLACTIN AND MACROPROLACTIN CONCENTRATIONS IN NORMAL SERA AFTER GEL-FILTRATION CHROMATOGRAPHY AND PEG IMMUNOPRECIPITATION

Measurement of the relative amounts of macroprolactin and monomeric prolactin in a subset of 10 randomly selected normal sera by gel-filtration chromatography revealed that macroprolactin makes up 2–9% of the total prolactin present. In contrast, applying the PEG immunoprecipitation method to the same 10 sera demonstrated a 64–70% recovery of prolactin.

COMPARISON OF HORMONE CONCENTRATIONS IN TRUE HYPERPROLACTINEMIC AND MACROPROLACTINEMIC INDIVIDUALS

In Table 1, we summarize the biochemical data derived from a retrospective chart review of two cohorts of patients identified as having either confirmed true hyperprolactinemia or confirmed macroprolactinemia. Total prolactin was similar in both groups. In the subgroup of patients in whom macroprolactin was not measured at the time of diagnosis, the interval between the initial measurement of prolactin and the retesting of archived sera [mean (SD)] was 5.6 (3.7) years. There was no significant difference between previously reported total prolactin values and those obtained on retesting the sera. After treatment with PEG, serum prolactin decreased from 1524 (202) mIU/L to 202 (27) mIU/L in macroprolactinemic patients, and from 2096 (233) mIU/L to 1705 (190) mIU/L in true hyperprolactinemic patients (P <0.01; Table 1). In the macroprolactinemic cohort, prolactin recoveries after PEG precipitation ranged from 2% to 37%, whereas those in the hyperprolactinemic group ranged from 71% to 99%. All of the hyperprolactinemic sera examined exhibited a decrease in prolactin after treatment with PEG, although

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Table 1. Clinical and laboratory data in true hyperprolactinemic and macroprolactinemic groups.[a]

Characteristics	Hyperprolactinemia (n = 42)	Macroprolactinemia (n = 21)
Age, years	30 (1)	28 (3)
Total prolactin,[b] mIU/L	2096 (233)	1524 (202)
Prolactin after PEG precipitation, mIU/L	1705 (190)	202 (27)[c]
FSH, IU/L	5.7 (0.5)	7.1 (2.1)
LH, IU/L	5.3 (0.5)	10.1 (2.4)[c]
Estradiol,[d] pmol/L	162 (33)	284 (48)[c]
Clinical features		
Oligomenorrhea or amenorrhea	84%	57%[c]
Galactorrhea	63%	29%[c]
Infertility	8%	29%
Headache	8%	10%
CT/MRI performed[e]	90%	93%
Abnormality identified	34%	15%
DA prescribed	88%	87%

[a] Data are mean (SE). Reference intervals: prolactin, 78–564 mIU/L; prolactin after PEG precipitation, 70–403 mIU/L; FSH, 2–25 IU/L; LH, 2–50 IU/L; estradiol, 110–1470 pmol/L.

[b] To convert prolactin mIU/L to μg/L, divide by 36.

[c] P <0.05 vs true hyperprolactinemic participants.

[d] To convert estradiol pmol/L to ng/L, divide by 3.67.

[e] Investigations and treatment carried out in participants in whom macroprolactin was measured retrospectively (n = 15).
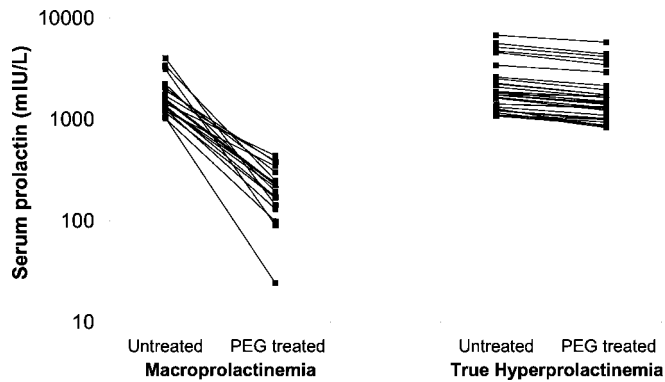
Fig. 1. Serum prolactin concentrations before and after treatment with PEG in patients with either macroprolactinemia or true hyperprolactinemia.

the effect was not as dramatic as that observed in the macroprolactinemic cohort (Fig. 1).

Serum estradiol and LH were significantly higher in macroprolactinemic patients (P <0.05; Table 1). Serum FSH did not differ between the two groups.

COMPARISON OF PRESENTING CLINICAL FEATURES, INVESTIGATION, AND TREATMENT IN TRUE HYPERPROLACTINEMIC AND MACROPROLACTINEMIC INDIVIDUALS

In both groups, oligomenorrhea or amenorrhea was the most frequent symptom at presentation, whereas galactorrhea, headache, and infertility occurred less frequently (Table 1). Whereas oligomenorrhea and galactorrhea 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).

Analysis was also undertaken of the investigation and treatment modalities used in the subgroup of patients in whom macroprolactin was measured retrospectively. This analysis was not carried out in patients in whom macroprolactin was measured at the time of presentation, because macroprolactinemia had been identified in this instance before decisions on additional investigations or treatment were made. Computed tomography (CT) or magnetic resonance imaging (MRI) was performed in 14 (93%) of 15 patients who were subsequently found to have macroprolactinemia and 38 (90%) of 42 patients with true hyperprolactinemia. Whereas the frequency of scanning did not differ between the groups, abnormalities were predominantly found in the hyperprolactinemia group (Table 1). Of the 38 scans performed in true hyperprolactinemic participants, 24 were nonpathologic, 7 revealed a microadenoma, and 7 revealed a macroadenoma. Microadenomas were seen in three participants with macroprolactinemia, but no macroadenoma was seen in this group.

Thirteen (87%) of 15 patients with macroprolactinemia and 37 (88%) of 42 patients with true hyperprolactinemia were treated with dopamine agonists (DAs). Treatment

with DA produced a decrease in prolactin from a mean of 1726 (279) mIU/L to 389 (98) mIU/L in the macroprolactinemic patients, and from 2393 (235) mIU/L to 309 (55) mIU/L in true hyperprolactinemic patients. Of 23 women with true hyperprolactinemia and oligomenorrhea or amenorrhea who were treated with DA, menses increased in frequency in 17, whereas an additional 2 became pregnant. In contrast, eight women with macroprolactinemia and oligomenorrhea or amenorrhea were treated with DA, but increased frequency of menses occurred in one woman only. Of 19 women who had true hyperprolactinemia and galactorrhea and who were treated with DA, symptomatic improvement occurred in 15. All four women with macroprolactinemia and galactorrhea who were treated with DA noted symptomatic improvement. In summary, therefore, DA was effective in treating galactorrhea in both true hyperprolactinemic and macroprolactinemic patients, but it increased menstrual frequency only in true hyperprolactinemic patients.

Discussion

True hyperprolactinemia is characterized by the presence of excess monomeric prolactin in serum. Macroprolactinemia in this study was defined by the presence of excess serum macroprolactin together with nonpathologic monomeric prolactin concentrations. The macroprolactin concentrations in hyperprolactinemic sera as determined by gel-filtration chromatography vary widely, ranging from 5% to 99% (23). Treatment of sera with high concentrations of PEG precipitates macroprolactin, and, although results have been shown to correlate well with gel filtration, macroprolactin concentrations obtained after PEG treatment are invariably higher (23, 25). Despite this discrepancy, laboratories screening for macroprolactin routinely rely on prolactin recoveries of <40% after treatment of sera with PEG to distinguish between true hyperprolactinemia and macroprolactinemia. The 40% threshold routinely used, however, is arbitrarily defined with little scientific basis. In certain cases, recoveries <40% may be consistent with true hyperprolactinemia. Olukoga and Kane (24) reported three patients with macroprolactinemia on the basis of recoveries <40% despite monomeric prolactin concentrations ranging from 1500 to 2000 mIU/L. Furthermore, distinguishing the two conditions by an absolute cutoff may not be possible, and it has been suggested that PEG recoveries of 30–65% should be classified as indeterminate and that those samples be subjected to gel-filtration chromatography for a definitive diagnosis (23).

In contrast to previous studies, the diagnosis of macroprolactinemia in this study was confined to those whose hyperprolactinemic sera, when treated with PEG, had a decrease in the prolactin concentration compared with that seen in sera from normoprolactinemic participants treated with PEG, i.e., <403 mIU/L. This approach leads to a more rigorous laboratory definition of macroprolactinemia than previously used by investigators who

used PEG precipitation, and it avoids any confusion as to whether biologically active prolactin is also present in excess when excess macroprolactin is present. It, furthermore, controls for the coprecipitation of monomeric prolactin that occurs when serum is treated with PEG. PEG treatment of sera from 110 healthy females produced a 5–44% decrease in prolactin in all sera. This effect, as assessed by gel-filtration chromatography, seems attributable to the precipitation of a significant variable amount of monomeric prolactin, together with any macroprolactin present in normal sera. The matrix effect of sera seems responsible for the coprecipitation of monomeric prolactin by PEG in that the recovery of Delfia prolactin standard after PEG treatment was almost quantitative.

The application of a prolactin reference interval for PEG-treated normal sera to hyperprolactinemic sera allowed the identification of two cohorts of patients: one with true hyperprolactinemia and the other in whom hyperprolactinemia could be accounted for entirely by macroprolactin. The results indicate that macroprolactinemic patients cannot be distinguished from patients with true hyperprolactinemia on the basis of clinical features alone. To our knowledge this is the first study to compare unselected macroprolactinemic patients with true hyperprolactinemic patients. Leslie et al. (14), in an uncontrolled case series, reviewed 55 consecutively presenting patients with macroprolactinemia and concluded that the clinical features of hyperprolactinemia were uncommon in this group. Valette-Kasic et al. (19) reported clinical and biochemical features of 106 patients with macroprolactinemia and concluded that menstrual abnormalities and galactorrhea occurred less frequently in patients with macroprolactinemia compared with patients with true hyperprolactinemia. The patients in the latter study, however, had been investigated for macroprolactinemia because of discrepant clinical, biochemical, or follow-up data and thus were not representative of an unselected macroprolactinemic population. Hauche et al. (26) identified macroprolactinemia in 46% of participants with hyperprolactinemia and observed that symptoms were more likely to occur in individuals with true hyperprolactinemia (90% vs 54%). The authors acknowledged that the particularly high incidence of macroprolactin in that study probably reflected the specialized nature of the study center, which received samples sent from other laboratories for confirmation of results that were difficult to explain in the clinical context. The current study demonstrated that, whereas oligomenorrhea and galactorrhea occurred more frequently in patients with true hyperprolactinemia, they also occurred in 57% and 29%, respectively, of macroprolactinemic patients. These differences, although statistically significant, are clearly not sufficient to distinguish between the two groups.

Serum estradiol and LH were significantly higher in individuals with macroprolactinemia compared with those with true hyperprolactinemia, which is consistent with previous reports that macroprolactin has limited

bioactivity (4–6, 27). Thus, it is likely that the association of the relatively common symptoms of galactorrhea and oligomenorrhea and the biochemical finding of macroprolactinemia observed in this and other studies (12, 14, 19) is coincidental. This is not surprising because it is these symptoms that will prompt measurement of prolactin. Thus, the clinician, unaware that hyperprolactinemia can be explained by the presence of macroprolactin, has an apparent explanation for the patient's symptoms. Failure to identify this situation has led to the inappropriate investigation and treatment of patients reported in the current study and in previously reported patients (20, 21, 24), one of whom underwent unnecessary pituitary surgical exploration (20). Similarly, more than 90% of our macroprolactinemic patients and 88% of those reported by Olukoga and Kane (12) underwent CT or MRI scanning to identify the cause of the hyperprolactinemia. Because ~10–20% of the general population demonstrate the presence of pituitary microadenoma at autopsy, it is not surprising that three macroprolactinemic patients in the current study were reported to have minor CT or MRI scan abnormalities consistent with the presence of a microadenoma (28). Consistent with this observation, Hauche et al. (26) observed that abnormal pituitary CT scans occurred in 21% of macroprolactinemic patients compared with 75% with true hyperprolactinemia. The presence of these abnormalities was probably incidental to the finding of macroprolactinemia and was not causally related. The observation that DA treatment was prescribed for 13 of the 15 retrospectively reviewed macroprolactinemic patients in the current study is consistent with a previous report, in which 13 of 17 macroprolactinemic patients received DA treatment (12). The decrease in prolactin concentrations and improvement of galactorrhea observed in macroprolactinemic patients on treatment with DAs may further mislead the unwary clinician. Improved galactorrhea does not indicate that patients were previously exposed to supraphysiologic concentrations of prolactin, because DA treatment also corrects galactorrhea in normoprolactinemic women (29). Although the present report is confined to observations in adult women, similar management problems have been reported in men (22) and children (30).

The variability of prolactin immunoassays to detect macroprolactin has been noted previously (9, 10, 31). Extensive investigations indicate that all tested assay systems detect macroprolactin (8). We have previously estimated that up to 10% of hyperprolactinemia reported in the United Kingdom may be attributed directly to the presence of macroprolactin (8, 32). In the US, this percentage is likely to be similar, given the widespread use of immunoassay systems with high cross-reactivity to macroprolactin reported by The College of American Pathologists (33). Our results indicate that, in clinical practice, macroprolactin accounting for hyperprolactinemia is a common cause of misdiagnosis, unnecessary investigation, and inappropriate treatment. The study laboratory

has now adopted the routine practice of reporting the concentration of macroprolactin and the concentration of prolactin corrected for macroprolactin in all hyperprolactinemic sera, together with a guide to interpretation. We recommend that routine screening of all hyperprolactinemic sera for the presence of macroprolactin be undertaken. If PEG immunoprecipitation is used, prolactin values obtained after precipitation should be compared with a reference interval derived by treating sera from healthy individuals in an identical manner.

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