Clinical characterization of patients with macroprolactinemia and monomeric hyperprolactinemia

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KEYWORDS
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Abstract Macroprolactinemia is often a cause of misdiagnosis, unnecessary expensive investigation, and unsuitable treatment. The aim of the present study was to investigate the clinical findings and the concentrations of macroprolactin in patients with hyperprolactinemia in our region. Eighty-four female hyperprolactinemic patients were screened for macroprolactinemia. Prolactin was measured by chemiluminesans method on an Immulite 2000 analyzer (Siemens Health Diagnostics, Deerfield, IL, USA). Recoveries less than or equal to 40% after polyethylene glycol precipitation were indicative of macroprolactinemia. Clinical features and biochemical values were compared in true hyperprolactinemic and macroprolactinemic patients. Macroprolactinemia was detected in 31 patients (36.9%), with 84 hyperprolactinemic female patients. There was no difference in frequency of galactorrhea and oligomenorrhea/amenorrhea between the two groups. When we evaluated the clinical features of patients according to prolactin levels, no significant difference was found between the groups. In conclusion, our initial data show that no clinical features could reliably differentiate macroprolactinemic from true hyperprolactinemic patients, but at least one of these symptoms was present in most macroprolactinemic patients.

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Introduction

Prolactin is a peptide hormone consisting of 199 amino acids with three intramolecular disulfide bonds and is secreted from acidophilic cells of the pituitary gland. Prolactin synthesized as a prehormone with a molecular weight of 26 kDa and proteolytically cleaved to mature polypeptide (monomeric form) has a molecular weight of 23 kDa [1]. The physiological effects of prolactin are the development of the breasts during pregnancy and stimulating lactation in postpartum women. Hyperprolactinemia has been characterized with galactorrhea, oligomenorrhea or amenorrhea, and infertility in women, and reduced libido, impotence, and galactorrhea in men [2,3]. Human serum prolactin circulates in multiple forms of different molecular sizes, including the biologically and...
immunologically active monomeric prolactin (little prolactin, 23 kDa) and biologically inactive forms dimeric prolactin (big prolactin, 50–60 kDa) and tetramer prolactin (big-big prolactin, 150–170 kDa) [4]. In normal serum, the major forms are monomeric prolactin (PRL) (85–95%) and dimeric PRL (10–15%), and the minor form is tetrameric prolactin (<1%). Big-big prolactin consists of an antigen–antibody complex of monomeric prolactin–immunoglobulin G and is currently defined as macroprolactin [5]. Macroprolactin has a long half-life in blood compared with normal prolactin and causes high concentrations of prolactin. Macroprolactin has limited biological activity and is currently defined as macroprolactin [5]. Macroprolactin has a long half-life in blood compared with normal prolactin and causes high concentrations of prolactin. Macroprolactin has limited biological activity in vivo, probably explained by changes in tertiary structure and the high molecular mass hindering the complex to cross the capillary walls [6,7]. Macroprolactinemia is often a cause of misdiagnosis, unnecessary expensive investigation, and unsuitable treatment [7,8].

The gold standard method of identifying macroprolactin by gel filtration chromatography of the serum is a time-, work-, and cost-intensive method not suited for screening analysis [9]. Therefore, simpler methods as alternatives to gel filtration chromatography for the screening of macroprolactinemia have been developed, including treatment of serum with polyethylene glycol (PEG), anti-human immunoglobulin G, and protein A [9]. The aim of the present study was to investigate the clinical findings and the concentrations of macroprolactin in patients with hyperprolactinemia in our region.

Materials and methods

The study included 84 female patients with hyperprolactinemia, who were consecutively evaluated at our institution for the subsequent determination of macroprolactin. Exclusion criteria included assumption of hyperprolactinemic drugs and presence of potentially hyperprolactinemic diseases, such as primary hypothyroidism, renal failure, major depression, and polycystic ovary syndrome. The study was approved by the ethical committee of our institution, and written informed consent was obtained from each subject.

Prolactin was measured by chemiluminesans method on an Immulite 2000 analyzer (Siemens Health Diagnostics, Deerfield, IL, USA). The reference range was 40–530 mIU/L in women and 53–360 mIU/L in men. The calibration range of the assay was up to 3,180 mIU/L, with an analytical sensitivity of 3.4 mIU/L. The intra-assay coefficient of variation (CV) values were 2.8%, 3.6%, 2.3%, and 2.5%, at the levels of 186.6 mIU/L, 402.6 mIU/L, 466.6 mIU/L, and 1,017 mIU/L. The corresponding interassay CV values were 8.2%, 7.4%, 5.9%, and 6.9%.

A total of 250 µL of serum was added to 250 µL of 25% PEG 6000 solution (Sigma-Aldrich Inc., Milan, Italy), mixed, and centrifuged for 30 minutes at 1,400 g at room temperature. A further 250 µL serum was added to 250 µL of a sample diluent. Prolactin was measured both in untreated serum and in the supernatant, and the results were expressed as percentage of prolactin recovery. Patients with a recovery less than 40% were classified as macroprolactinemic.

All statistical calculations were performed using SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, USA). Quantitative variables were reported in the text as mean ± standard deviation. Comparison of clinical and biochemical characteristics was made by the χ2 test for categorical variables and the Students’ paired and unpaired t tests, Mann–Whitney U test, and Kruskal–Wallis nonparametric analysis of variance for continuous variables. Two-tailed p value less than 0.05 was considered statistically significant.

Results

Serum samples were obtained from 31 patients with macroprolactinemia (Group A), defined as having hyperprolactinemia. A group of hyperprolactinemic patients (n = 53) with the absence of macroprolactin was considered a group of true hyperprolactinemic patients (Group B). Macroprolactinemia was detected in 31 patients (36.9%), with 84 hyperprolactinemic female patients. Mean prolactin in patients with macroprolactinemia was 1,354.6 mIU/L, and in hyperprolactinemic patients without macroprolactinemia, it was 2,018.2 mIU/L. Galactorrhea and oligomenorrhea/amenorrhea were more common in patients with the absence of macroprolactin. There was no difference in the frequencies of galactorrhea and oligomenorrhea/amenorrhea between the two groups (Table 1). When we evaluate the clinical features of patients according to the prolactin levels, no significant difference was found between Group 1 [clinical feature (+) and macroprolactin (−)] and Group 2 [clinical feature (−) and macroprolactin (−)] (Fig. 1). There were no significant

| Table 1 | Comparison of biochemical and clinical values among patients |
|-----------------|-----------------|-----------------|-----------------|
| Characteristics | Group A (n = 31) | Group B (n = 53) | p |
| Age, yr<sup>a</sup> | 29.4 ± 9.9 | 33.0 ± 10.9 | NS |
| Prolactin, mIU/L<sup>a</sup> | 1,354.6 ± 1,032.4 | 2,018.2 ± 1,734.1 | <0.05 |
| Post PEG prolactin, mIU/L<sup>a</sup> | 269.2 ± 235.3 | 1,386.4 ± 1,157.5 | <0.0001 |
| Asymptomatic patient, % | 16.9 | 6.4 | <0.05 |
| Galactorrhea, % | 40.9 | 52.8 | NS |
| Oligomenorrhea/amenorrhea, % | 68.1 | 54.7 | NS |

<sup>a</sup> Data are presented as mean ± standard deviation.

Group A: increased prolactin levels with macroprolactin and Group B: increased prolactin levels in the absence of macroprolactin. NS = not significant; SD = standard deviation; PEG = polyethylene glycol.
Figure 1. Comparison of prolactin levels (mean ± standard deviation) according to the clinical features. Group 1 = clinical feature (+), macroprolactin (−); Group 2 = clinical feature (−) macroprolactin (−); Group 3 = clinical feature (+), macroprolactin (+); Group 4 = clinical feature (−), macroprolactin (+).
differences in clinical features between Group 3 [clinical feature (+) and macroprolactin (+)] and Group 4 [clinical feature (−) and macroprolactin (+)] (Fig. 1).

Discussion

Macroprolactin is common in patients with hyperprolactinemia, but the incidence of macroprolactinemia is not known precisely. The incidence of macroprolactinemia ranges from 10%–46% of samples from these patients [10, 11]. Valette-Kasic et al. [10] identified macroprolactinemia in 10% of patients with hyperprolactinemia, and the low incidence was attributable to selection bias. Hauache et al. [11] found the highest incidence of macroprolactinemia (46%). The authors attribute this high incidence to the nature of the study center, which received samples sent from other laboratories for confirmation of results. Vieira et al. [12] found macroprolactin to be prevalent in 36% of the 1,279 samples with PRL more than 540 mU/L. In our study, macroprolactin was found at a frequency of 36.9% of the hyperprolactinemic patients (>530 mU/L) based on the limit of less than 40% recovery after PEG precipitation. In our opinion, this discrepancy in studies depends on patient selection, threshold for measuring prolactin, limit of recovery used, and the type of immunochemical method. Furthermore, the high prevalence of macroprolactinemia in our patients might also be because of the fact that our hospital is a center for unexpected hormone results that are sent from other hospitals for confirmation.

Hyperprolactinemic patients usually have galactorrhea, menstrual irregularity, and infertility. In our study, 16.9% of the patients with macroprolactinemia had no symptoms of hyperprolactinemia. Conversely, 6.4% of the patients with true hyperprolactinemia were asymptomatic. According to our results, the occurrence of the symptoms shows asymptomatic hyperprolactinemia with a predominance of macroprolactin in the circulation. Biological activity of macroprolactin is controversial. First reports on macroprolactin in the NB2 lymphoma cell bioassay showed lower biological activity [13], but in recent studies, normal bioactivity of macroprolactin was shown in the NB2 assay [14]. Leslie et al. [15] reviewed 55 consecutively presenting patients with macroprolactinemia and concluded that the clinical features of hyperprolactinemia were unusual in this group. Valette-Kasic et al. [10] found that galactorrhea and menstrual abnormalities were significantly less frequently associated in the macroprolactinemic patients compared with the hyperprolactinemic patients with a normal PRL chromatography. Suliman et al. [7] reported that oligomenorrhea and galactorrhea occurred more frequently in patients with true hyperprolactinemia (84% and 63%, respectively) than in macroprolactinemic patients (57% and 29%, respectively). In our data, the clinical findings leading to the diagnosis of macroprolactinemia, including menstrual disorders and galactorrhea, were not significantly different from those of true hyperprolactinemic patients. Taking these findings into account, PEG has proved to be a useful reagent in distinguishing macroprolactinemia from true hyperprolactinemia, but one should always keep in mind that macroprolactinemic patients cannot be distinguished from patients with true hyperprolactinemia on the basis of clinical features alone.

In conclusion, our initial data show that no clinical features could reliably differentiate macroprolactinemia from true hyperprolactinemic patients, but at least one of these symptoms was present in most macroprolactinemic patients. Also, we recommend screening macroprolactinemia in all hyperprolactinemic patients for avoiding unnecessary further investigations, which would result in cost saving and accurate diagnosis.

References