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ORIGINAL ARTICLE

Prevalence of pituitary adenomas in macroprolactinemic patients may be higher than it is presumed

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Abstract One form of prolactin (PRL) is macroprolactin with high molecular mass. Many macroprolactinemic patients have no pituitary adenomas and no clinical symptoms of hyperprolactinemia, it is controversial whether macroprolactinemia is a benign condition that does not need further investigation and treatment. In this study, we aimed to compare macroprolactinemic patients (group I) with the true hyperprolactinemic patients (group II) for the presence of pituitary adenoma. We investigated 161 patients with hyperprolactinemia, whose magnetic resonance imaging records of the pituitary were taken. All patients were questioned for irregular menses, infertility and examined for galactorrhea. Patients were screened for macroprolactinemia by polyethylene glycol precipitation, and a recovery of $\leq$40% and normal monomeric PRL level was taken as an indication of significant macroprolactinemia. Of 161 patients with hyperprolactinemia, 60 (37.26%) had macroprolactinemia. PRL levels of group II were lower than those of group I ($P = 0.011$), although monomeric PRL levels of group II were higher than those of group I ($P = 0.0005$). Of 60 macroprolactinemic patients, 16 (26.7%) had pituitary adenomas. The prevalence of pituitary adenomas was lower in group I, compared with group II ($P = 0.0005$). No significant differences were found between the prevalences of irregular menses and infertility of group I and II ($P = 0.084$, $P = 0.361$). Prevalence of galactorrhea in group I was lower than that in group II ($P = 0.048$). Prevalence of pituitary adenomas in macroprolactinemic patients is lower compared with the true hyperprolactinemic patients, but may be higher than that found in other recent studies and in the general population.

Keywords Macroprolactinemia · Pituitary adenoma · Hyperprolactinemia

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Introduction

Prolactin (PRL) is a polypeptid hormone which circulates in three discrete forms. These include a monomer with molecular mass of 23 kDa, which accounts for approximately 85% of PRL present in normal individuals, a 50 kDa species accounting for 10−15%, and a small but variable amount of a high molecular mass form (150−170 kDa) termed big big prolactin or macroprolactin. Macroprolactin is predominantly made up of PRL complexed with immunoglobulin, although a small proportion may be heteromers [1–5].

In about 15–26% of patients with hyperprolactinemia, the elevated PRL level is attributed to macroprolactin; this phenomenon has been referred to as macroprolactinemia [5].

Having reduced biological activity, macroprolactinemia is suggested to have a few or no clinical symptoms and neuroradiological features of hyperprolactinemia caused by monomeric PRL. However, several authors have pointed out that some macroprolactinemic patients do have clinical symptoms of hyperprolactinemia and also evidence of pituitary adenomas [2, 5–9].

It is not clear yet, whether pituitary imaging should be used for all patients with macroprolactinemia or not. Management and investigation of patients with macroprolactinemia and especially administration of dopamine agonists to those patients, are controversial.

The aim of our study was to examine the presence of pituitary adenomas in macroprolactinemic patients by comparing macroprolactinemic patients to the patients with true hyperprolactinemia, to assist in designing the format of future investigation and management protocols.

Patients and methods

This study was approved by our institutional ethics committee and the study subjects gave informed consent to participate in the study.

We studied 434 patients whose serum PRL levels were measured in our biochemistry laboratory between July 2004 and August 2005. Samples from women with a PRL value >24.1 ng/ml were precipitated with polyethyleneglycol (PEG) to investigate for the existence of macroprolactinemia.

Patients receiving pharmacologic agents that cause elevated or altered PRL levels or who had hypothyroidism, diagnosis or symptoms of polycystic ovarian syndrome, renal or liver disorders, intercostal nerve stimulation, or pituitary stalk injury due to trauma or surgery, were excluded from the study.

All patients were questioned for infertility and regularity of menses, examined for galactorrhea, and magnetic resonance imaging (MRI) of the pituitary was taken for all patients. Anterior pituitary hormones of all the patients were also determined.

PRL assay and other laboratory investigation

Serum PRL, free thyroxine (T4, reference interval: 0.93−1.7 ng/dl), thyroid stimulating hormone (TSH, reference interval: 0.27−4.2 μIU/ml), luteinizing hormone (LH, reference interval for follicular phase: 2.4−12.6 mIU/ml), follicule stimulating hormone (FSH, reference interval for follicular phase: 3.5−12.5 mIU/ml), estradiol (reference interval for follicular phase: 12.5−166 pg/ml), and cortisol (>18 mg/dL before 8.30 a.m. is accepted for reference range) levels were measured by electrochemiluminescent immunoassay (ECLIA) (Elecsys, Modular Analytics, Roche Diagnostics) during early follicular phase.

PEG precipitation test

Macroprolactin assessment was performed by PEG precipitation of serum samples with PRL levels exceeding the upper limit of the normal reference range (PRL>24.1 ng/ml). The method which has been previously described by Hattori et al. [10] and extensively validated by Olukago and Kane [11] was performed as follows: 200 μl of serum was added to 200 μl of 25 g/dl PEG 6000 solution. After thorough mixing and centrifugation at 3000 rpm for 30 min, the supernatant was removed for analysis, and PRL assay was performed immediately. PRL in the supernatant was considered to be free of macroprolactin, because PEG precipitates PRL molecules with a molecular weight more than 100 kDa.

The recovered amount of monomeric PRL (%) was derived for each serum as a percentage of the PRL measured in the supernatant relative to that measured in the untreated serum.

In this study, as in many other studies [10–13], after the PEG precipitation test, recovered amount of monomeric PRL ≤40% was taken as an indicator for the presence of macroprolactin. However, in some macroprolactinemic patients, excess biologically active monomeric PRL was present along with macroprolactin. Macroprolactin is a well-known source of immunoassay interference and leads to misdiagnosis of hyperprolactinemic patients. Beltran et al. had studied serum samples treated with PEG to establish and validate reference intervals for total and monomeric PRL on various immunoassay platforms. They determined the upper limit of normal as 381 mIU/l (17.96 ng/ml) for monomeric PRL after PEG precipitation on Elecsys (Roche Diagnostics), the same immunoassay platform that we used [12]. Our priority was to determine whether monomeric PRL concentrations were increased and we accepted the patients who had supraphysiological concentrations of monomeric PRL (>17.96 ng/ml) as true hyperprolactinemic patients even if the recovered amount of monomeric PRL was ≤40% after PEG precipitation. Therefore, all patients with hyperprolactinemia who had monomeric PRL levels <17.96 ng/ml and recovered amount of monomeric PRL ≤40% of total PRL were labeled as macroprolactinemic patients.

Statistical analysis

Comparison of MRI findings and hyperprolactinemic symptoms (irregular menses, infertility, galactorrhea) of the patients with true hyperprolactinemia, with those of macroprolactinemic patients, and also comparison of hyperprolactinemic symptoms of macroprolactinemic patients with and without pituitary adenomas, were performed by the Chi-square test. Mann−Whitney *U* test was used to compare PRL and monomeric PRL levels of the macroprolactinemic patients who had pituitary adenomas and who did not. Fisher's exact test was used to compare the prevalences of hyperprolactinemic symptoms of

macroprolactinemic patients with and without pituitary adenomas. Results were expressed as mean, and statistical significance was set at a level of 0.05.

Results

In our study, 176 of 434 patients, whose PRL levels were measured, had hyperprolactinemia. Fifteen patients with hyperprolactinemia were excluded from the study for the following reasons: seven of them had hypothyroidism, one of them had renal failure, three of them were receiving pharmacologic agents that elevate PRL levels, and four of them were thought to have polycystic ovarian syndrome. Sera from 161 patients with hyperprolactinemia were tested for macroprolactinemia. All patients who had irregular menses and/or infertility were examined by the gynecologist and mammarian ultrasonography, mammography, and MRI were applied to the patients who had galactorrhea and no explanation for these symptoms and signs but hyperprolactinemia could be found.

Of the 161 patients with hyperprolactinemia, 60 (37.26%) had macroprolactinemia and 101 (62.73%) had hyperprolactinemia mainly due to monomeric PRL. There were no significant differences between the ages of patients with true hyperprolactinemia and those of the patients with macroprolactinemia ($P = 0.213$). Serum monomeric PRL levels of the patients with true hyperprolactinemia were significantly higher than those of the macroprolactinemic patients ($P = 0.0005$), although serum total PRL levels of the patients with true hyperprolactinemia were significantly lower than those of the macroprolactinemic patients ($P = 0.011$). In contrast to the expectation, no significant differences were found between the prevalences of irregular menses and infertility of the patients with macroprolactinemia and true hyperprolactinemia ($P = 0.084$ and $P = 0.361$, respectively) (Table 1). However, the prevalence of galactorrhea in patients with macroprolactinemia was lower than that in patients with true hyperprolactinemia ($P = 0.048$).

Pituitary adenomas were identified in the MRIs of 16 (26.7%) macroprolactinemic patients and of 56 (55.4%) patients with true hyperprolactinemia. Pituitary adenomas were less common in patients with macroprolactinemia compared with the patients with true hyperprolactinemia ($P = 0.0005$) (Table 1). Except one of them, all the pituitary adenomas of the macroprolactinemic patients were microadenomas. One patient with macroprolactinemia who had pituitary macroadenoma, had a 12 mm macroadenoma. There were no significant differences between PRL and monomeric PRL levels of macroprolactinemic patients with and without pituitary adenomas ($P = 0.880$, $P = 0.993$, respectively) (Table 2). PRL and monomeric PRL levels of the patient with macroprolactinemia who had 12 mm adenoma were 51.2 and 8.2 ng/ml, respectively. This patient had no hyperprolactinemic symptoms (irregular menses, infertility, galactorrhea). Her other anterior pituitary hormones were normal (FreeT4: 1,1 ng/dl, TSH: 1.8 μIU/ml, LH: 8.2 mIU/ml, FSH: 11.4 mIU/ml, estradiol: 64.8 pg/ml, basal cortisol: 18.4 mg/dl and after 1 mg dexametasone supression test cortisol level was 1.1 mg/dl).

There were no significant differences between the prevalences of irregular menses, infertility, and galactorrhea in macroprolactinemic patients with and without pituitary adenomas ($P = 0.710$, $P = 689$, and $P = 0.096$, respectively) (Table 2).

Discussion

In the present study, the prevalence of macroprolactinemia is found to be 37.26% in hyperprolactinemic patients. This high prevalence in our study probably reflects selection bias because of the specialized nature of our study center. In the study, nine patients were found to have >60% of total PRL as macroprolactin, but these nine patients were

Table 1 Clinical and laboratory data of the patients with true hyperprolactinemia and macroprolactinemic patients

	Patients with true hyperprolactinemia ($n = 101$)	Macroprolactinemic patients ($n = 60$)	P
Characteristics			
Mean age (year)	34.05 ± 12.96	36.70 ± 13.05	0.213
Mean total PRL (ng/ml)	107.83 ± 142.47	129.119 ± 106.73	0.011
Mean m-PRL (ng/ml)	73.19 ± 115.64	12.90 ± 4.64	0.0005
Pitutary imaging			
Pitutary adenomas (%)	55.4	26.7	0.0005
Clinical features			
Galactorrhea (%)	29.7	15	0.048
Irregular menses (%)	30.7	18.3	0.084
Infertility (%)	20.8	15	0.361

Table 2 Clinical and laboratory data of the macroprolactinemic patients with and without pituitary adenoma

	Macroprolactinemic patients with pituitary adenoma ($n = 16$)	Macroprolactinemic patients without pituitary adenoma ($n = 44$)	P
Characteristics			
PRL (ng/ml)	130.09 ± 112.6	126.43 ± 91.93	0.880
m-PRL (ng/ml)	12.91 ± 4.57	12.89 ± 5	0.993
Clinical features			
Irregular menses (%)	12.5	20.5	0.710
Infertility (%)	18.8	13.6	0.689
Galactorrhea (%)	0	20.5	0.096

accepted to be true hyperprolactinemic patients as they had elevated levels of monomeric PRL. Therefore, if we had used only the 40% method of labeling for macroprolactin, we would have missed 15% of samples with elevated levels of monomeric PRL. It was interesting to find the prevalence of pituitary adenomas as 26.7% in macroprolactinemic patients, this is higher than that found in other recent studies and in the general population [1, 4, 9, 11], although macroprolactinemic patients were not selected in our study. However, the prevalence of pituitary adenomas was found to be lower in patients with macroprolactinemia than that in patients with true hyperprolactinemia. In our study, it was interesting that macroprolactinemic patients had hyperprolactinemic symptoms such as irregularity of menses and infertility as frequent as patients with true hyperprolactinemia, although none of them had high monomeric PRL levels. However, the prevalence of galactorrhea in macroprolactinemic patients was lower than that in patients with true hyperprolactinemia.

Macroprolactinemia has been suggested to be a benign condition that does not need treatment or further investigation. [1, 5, 14, 15].

The nature of macroprolactin is still unclear, however, recent evidence indicates that macroprolactin is a complex of the 23 kDa PRL with an IgG molecule. Because of the lack of symptoms associated with true hyperprolactinemia in the majority of macroprolactinemic patients and the finding that macroprolactin exhibits normal in vitro bioactivity when tested in Nb2 cells, it has been proposed that macroprolactin cannot exert full biological activity in vivo. For a long time, the large size of macroprolactin has been proposed to make it unable to cross capillary membranes to reach its target receptors, thus reducing its in vivo activity and explaining the attenuated clinical manifestations [1, 15–18]. However, results of recent studies have shown that macroprolactin has reduced activity toward its homologous receptor and this altered bioactivity may contribute to the absence of symptoms related to macroprolactin [19, 20].

Macroprolactin has recently been demonstrated in 15−26% of patients with hyperprolactinemia [5]. Numerous case reports of patients with high levels of circulating macroprolactin but few or no clinical and radiological findings of hyperprolactinemia such as amenorrhea, galactorrhea, infertility, and pituitary adenoma have led to the assumption that macroprolactinemia is a benign condition that does not need treatment or further investigation. Normal pituitary imaging is very likely to be found in most asymptomatic patients with macroprolactinemia [14, 15, 21]. Therefore, many authors suggest that if all samples showing hyperprolactinemia are tested for macroprolactin, unnecessary anxiety and costly medical procedures may be prevented [5, 14, 15, 22–24].

However, if we consider that 21.1% of macroprolactinemic patients had abnormal imaging findings reported by Hauache et al. [9], it would be unwise to conclude that patients with macroprolactinemia may not require pituitary imaging. Schlechte and some other authors have suggested that most women with macroprolactinemia do not have the typical symptoms of hyperprolactinemia, but some have amenorrhea or galactorrhea and the presence of macroprolactin does not rule out pituitary adenoma [16, 25–28]. In 2001, Leslie et al. [25] found macroprolactinemia in 26% of 1,225 patients with hyperprolactinemia, but clinical data were available in only 55 patients with macroprolactinemia: they found classic hyperprolactinemic symptoms in 27% of those patients with macroprolactinemia and five of them were found to have pituitary adenomas. However, the weakness of their study was that all macroprolactinemic patients with pituitary adenomas had supraphysiological levels of monomeric PRL. Confirming Leslie's findings, Gibney et al. concluded that although oligomenorrhea/amenorrhea and galactorrhea were more common in patients with true hyperprolactinemia, they were also frequently present in macroprolactinemic patients. Therefore, they suggested that macroprolactinemic patients could not be differentiated from true hyperprolactinemic patients on the basis of clinical features alone [29].

In the present study, we found that 15% of macroprolactinemic patients had galactorrhea, 18.3% of macroprolactinemic patients had irregular menses, 15% of

macroprolactinemic patients had infertility. Different from other studies [4, 25, 30], we found that macroprolactinemic patients had hyperprolactinemic symptoms such as irregular menses and infertility as frequent as patients with true hyperprolactinemia, however, the prevalence of galactorrhea was higher in patients with true hyperprolactinemia.

In the present study, we determined that 26.7% of macroprolactinemic patients had pituitary adenomas, although none of them were proven by histology as prolactinomas. Our findings confirm Bağdatoğlu's findings which determined the prevalence of pituitary adenomas in macroprolactinemic patients as 30% [22]. Bağdatoğlu et al. determined macroprolactinemia when recovered amount of monomeric PRL was ≤40% of total PRL level. However, the weakness of their study was that they missed 46.15% of samples with elevated levels of monomeric PRL. 6 out of 13 patients labeled as macroprolactinemic, had supraphysiological levels of monomeric PRL [12, 22].

10–20% of CT/MRI studies performed for reasons other than suspected pituitary disease reveal images that are consistent with the presence of pituitary adenomas. Autopsy findings also confirm this prevalence. In our study, the prevalence of pituitary adenomas was higher than that found in other recent studies and in the general population [1, 4, 9, 11, 23, 24, 30–33].

Some studies have reported that the existence of a prolactinoma might be associated with the presence of macroprolactinemia. In a series of 106 patients with macroprolactinemia studied by Valette-Kasic et al., five cases of prolactinoma were identified and proven by histology. Serum monomeric PRL levels of those patients were 44, 84, 32, 32, 27 μg/l, respectively (All were supraphysiological levels for monomeric PRL) and their monomeric PRL levels were ≤40% of serum total PRL levels [26]. In another study performed by Olukago and Kane [11] in 13 macroprolactinemic patients, three adenomas were found by pituitary imaging, none of them were proven histologically to be prolactinomas, however, it is important that none of the macroprolactinemic patients had high monomeric PRL levels. In 1998, Tritos presented two men with macroprolactinemia and one of these patients had pituitary adenoma that stained positively for PRL by immunohistochemistry. His serum PRL level was 46620 mU/l and macroprolactin level was 53% of serum total PRL level [8]. Hyperprolactinemic symptoms of that patient could be due to the supraphysiological levels of monomeric PRL. Therefore, it may be a mistake for that patient to mention the relationship of macroprolactinemia and pituitary adenoma and hyperprolactinemic symptoms. In our study, MRIs of patients showed that 25% of patients with macroprolactinemia had pituitary microadenomas and 1.67% of patients with macroprolactinemia had pituitary macroadenomas. It is the weakness of our study that none of the adenomas was proven histologically to be prolactinomas as there was no indication for surgery in these patients. However, one of the important findings of our study was that all the macroprolactinemic patients with microadenomas and one of the macroprolactinemic patients with macroadenoma did not have high monomeric prolactin levels, but had high macroprolactin levels. Serum PRL and monomeric PRL levels of the macroprolactinemic patient with a 12 mm adenoma were 51.2 and 8.2 ng/ml, respectively. As the monomeric PRL level of that patient was not high, her pituitary adenoma might be a pituitary macroadenoma causing macroprolactinemia. In addition, that patient had no hyperprolactinemic symptoms (irregular menses, infertility, or galactorrhea).

In 2003, Mounier et al. determined unusual immunocytochemical feature of deposits of PRL aggregates in one of the patients with macroprolactinemia. Serum PRL and monomeric PRL levels of that patient were 201 and 38 ng/ml, respectively. This finding may suggest the tumoral origin of macroprolactin, although monomeric PRL level of that patient was high [34]. Their findings were in agreement with those of Ohnami et al., who on the basis of the similarity of the chromatographic PRL patterns of tumoral extracts and serum samples from eight patients, concluded that these large forms of PRL were possibly secreted by a pituitary adenoma. They also found that the ratio of macroprolactin to monomeric PRL in the tumor extract (38.2 ± 3.6%) was significantly larger than that in normal pituitary extract (5.8 ± 2.8%) [35].

In conclusion, macroprolactinemia should not be ignored for further investigation, because a pituitary adenoma might be present. However, the prevalence of pituitary adenomas is lower in patients with macroprolactinemia than that in patients with true hyperprolactinemia. In contrast to the expectation, patients with macroprolactinemia may have some hyperprolactinemic symptoms such as irregularity of menses and infertility as frequent as patients with true hyperprolactinemia. Therefore, macroprolactinemic patients should not be differentiated from true hyperprolactinemic patients on the basis of clinical features alone.

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