CLINICAL EXPRESSION OF BIG-BIG PROLACTIN AND INFLUENCE OF MACROPROLACTINEMIA UPON IMMUNODIAGNOSTIC TESTS

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In some humans, the big and big-big prolactin variants represent the majority of circulating prolactin, considered to be without biological activity. Aims: to establish the clinical expression of macroprolactinemia and the interference with immunodiagnostic tests in a randomized group of 84 consecutive patients with hyperprolactinemia. IRMA and electrochemiluminescence (Elecsys) were used for PRL assay; gel filtration chromatography (GFC) and protein A precipitation test were used to reveal macroprolactinemia. Results: Macroprolactinemia was found in 16 out of 84 patients (group A), 62 patients had hyperprolactinemia of other causes (group B) and 6 had normal PRL levels and normal GFC (group C). Of 16 patients with macroprolactinemia, 6 showed normal PRL with IRMA and hyperprolactinemia with Elecsys. The difference between the two methods used (Δ = PRL determined by Elecsys, -PRL determined by IRMA) correlated with big big PRL level determined by GFC with Elecsys in all patients. The strongest correlation was found in patients with macroprolactinemia (group A, $r=0.82$, $p<0.01$) as compared with group B, without macroprolactinemia ($r=0.39$, $p<0.01$). Menstrual disorders were expressed, but less frequent in group A versus B (3/15 vs. 28/56, $p=0.04$), and the appearance of galactorrhea and infertility were not statistically different. Conclusions: In these patients, macroprolactinemia had clinical expression, but weaker than in true hyperprolactinemic patients. It determines high apparent variability of serum PRL level in current commercial assays.

Key words: macroprolactinemia, big-big prolactin, immunoassay, hyperprolactinemia.

INTRODUCTION

Prolactin is a polypeptide hormone produced mainly in anterior pituitary lactotrophs, but also in extra pituitary tissues, as in decidua, myometrium, breast, prostate, brain and immune cells, functioning as a hormone and a cytokine (1).

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There are three major circulating variants of prolactin, as detected by gel filtration chromatography (GFC): monomeric form ("little prolactin", 23 kD), which normally is up to 85-90% of serum prolactin, big prolactin (50-60 kD, <10%) and big-big prolactin (>100 kD, <3%) (Fig. 1). In some humans, the big-big variant represents the majority of circulating prolactin, situation called macroprolactinemia (2). Big prolactin is a complex of little prolactin and another serum component, possible prolactin-binding protein, as suggested by some authors (3), or represents a dimmer of little prolactin (4).

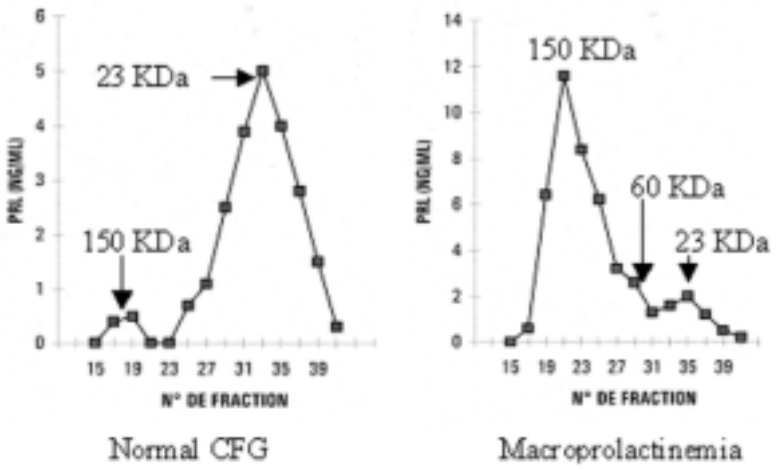

Figure 1. The three major circulating variants of prolactin, as detected by gel filtration chromatography: monomeric form (23 kD), big prolactin (50-60 kD), and big-big prolactin (150 kD).

Big-big prolactin, also called macroprolactin, is mainly due to a complex of peripherical origin from monomeric prolactin of any source (pituitary or extra pituitary) and immunoglobulin G (5-7). However, there are patients with macroprolactinemia who lack anti-PRL antibodies (8, 9). Because of its low clearance, macroprolactinemia determines high levels of PRL with normal pituitary function. This complex has different immunoreactivity in available commercial assays, causing great variability in serum prolactin (10, 11).

The most frequent causes of high levels of prolactin, when pregnancy is excluded, are pituitary tumors, drugs and primary hypothyroidism (12). Macroprolactinemia is more common than generally believed; its prevalence has been reported to be up to 46% of hyperprolactinemias (13-16). It is more frequent in patients with autoimmune diseases, such as in systemic lupus erythematosus, where it could represent a prognostic factor (17, 18).

The clinical consequences of macroprolactinemia are still a matter of debate. First, high molecular weight variants of prolactin were found in 1981 in an acromegalic patient with hyperprolactinemia (19). Many studies reported predominance of big-big prolactin in patients with normal gonadic function (20-24). However, there are patients who present some of the classical symptoms of hyperprolactinemia (25-29).

The aim of this study is to establish the clinical expression of macroprolactinemia and its influence upon immunodiagnostic assays.

MATERIALS AND METHODS

Eighty-four consecutive patients were investigated for hyperprolactinemia in the Department of Endocrinology, Timone Hospital, Marseille. All patients had a complete clinical evaluation, laboratory tests (basal prolactin (PRL) levels and after dynamic tests, FSH, LH and LHRH test, fT3, fT4, TSH, thyroid peroxidase and thyroglobulin antibodies), neuroradiological examination (MRI, CT). PRL levels were measured using an immunoradiometric method (IRMA) and by electrochemiluminescence (Elecsys).

To establish macroprolactin percents, GFC and protein A precipitation test were used. Chromatographic method was described elsewhere (30). Gel filtration revealed three peaks of PRL: >100 kD (big-big prolactin), 50-60 kD (big prolactin) and 23 kD, monomeric PRL. Patients who had >50% of prolactin in big and big-big fractions were considered to have macroprolactinemia. Precipitation method consisted in measuring prolactin before and in the supernatant obtained after precipitation with a protein A- Sepharose suspension (Immunotech Beckman Coulter); the percent of macroprolactin could be estimated using the difference between these two values: 100 (PRL before- PRL after X 2.3) / PRL before.

Statistical analysis: data were expressed as mean $\pm$ SD. Groups were compared using t test for continuous variables and χ^2 test for qualitative variables. Results were considered significant when $p<0.05$. Pearson correlation test was used for r determination.

RESULTS

Hyperprolactinemia was due to macroprolactinemia in 16 patients (19%, A group). Other causes of hyperprolactinemia (B group) were: pituitary adenoma (33 patients; 28 with prolactinoma), iatrogenic causes (6 patients: 5 after pill and 1 after domperidon), PCOS (n=3); pituitary abscess, hydrocephaly, astrocytoma (each one patient). 17 cases had idiopathic hyperprolactinemia (Fig. 2). Six patients were found normoprolactinemic (control C group).

Clinical characteristics of patients in the studied groups are illustrated in table 1. Of 16 patients with macroprolactinemia, 6 were found to have normal PRL level and 10 patients had PRL level>20 ng/ml, as determined by IRMA.

Sex ratio was not statistically different between groups, but patients in macroprolactinemic group tended to be older than in B and C groups. The reasons for prolactin determination were: menstrual disorders, including amenorrhea,

galactorrhea, infertility, others: gynecomasty, mastodynia, headache, weakness, assessment for pill, sexual dysfunction, hirsutism. Menstrual disorders were statistically less frequent in macroprolactinemic women than in hyperprolactinemic women with normal chromatographic pattern (p=0.04), not different from patients with normal prolactin level (p=NS). Amenorrhea was found in 4 (27%) macroprolactinemic women, but 3 were postmenopausal, with elevated serum gonadotropins and 1 had hyperandrogenism, with normal gonadotropins level.

There were 3 patients with galactorrhea in A group, 1 with normal prolactin

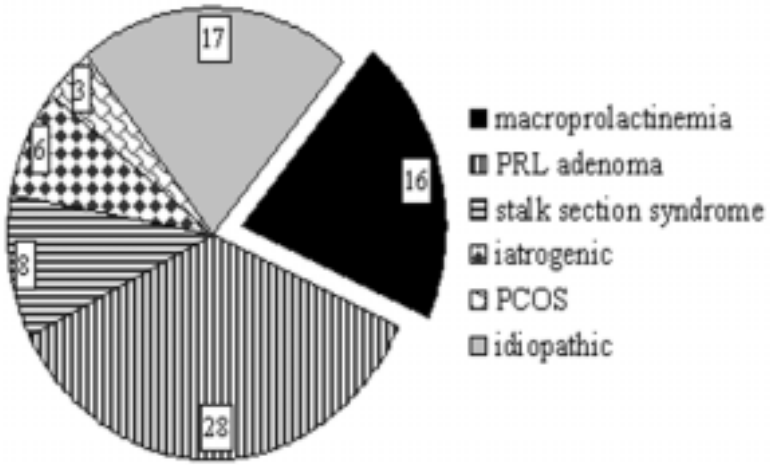

Figure 2. Etiology of hyperprolactinemia in studied groups; PCOS -polycystic ovary syndrome.

Table 1. Clinical characteristics of the studied groups

	A group (Macro PRL)	**B group** (other HPRL)	**C group** (normal PRL)
Number of patients	16	62	6
Sex ratio (F/M)	15/1	56/6	6/0
Age (X SD) years	40.6± 8.9 *, **	33 ±10.2	34.5 7.2
Menstrual disorders	3(19%)*	28(45%)	2(33%)
Amenorrhea	0	8(13%)	0
Galactorrhea	3(19%)	26(42%)	3(50%)
Infertility	6(37%)	23(37%)	3(50%)

*p<0.05 A *vs*. B group, ** p<0.05 A *vs*. C group, Macro PRL -macroprolactinemia, Other HPRL - other causes of hyperprolactinemia.

level. Galactorrhea was less frequent than in B group (p=0.04), but similar to control group C (5 patients). Infertility determined PRL measuring in 6 patients from A group, 3 with secondary infertility (they had previously given birth to 1-2 children) and 3 nulliparous women, all over 34 years of age. 3/6 patients in control group had infertility, and in all who had gonadotropins determination, these were found normal. The reason of the first presentation for the male who had macroprolactinemia was left gynecomasty, without galactorrhea (Fig. 3).

Although macroprolactinemia appears to be more frequent in immune disorders

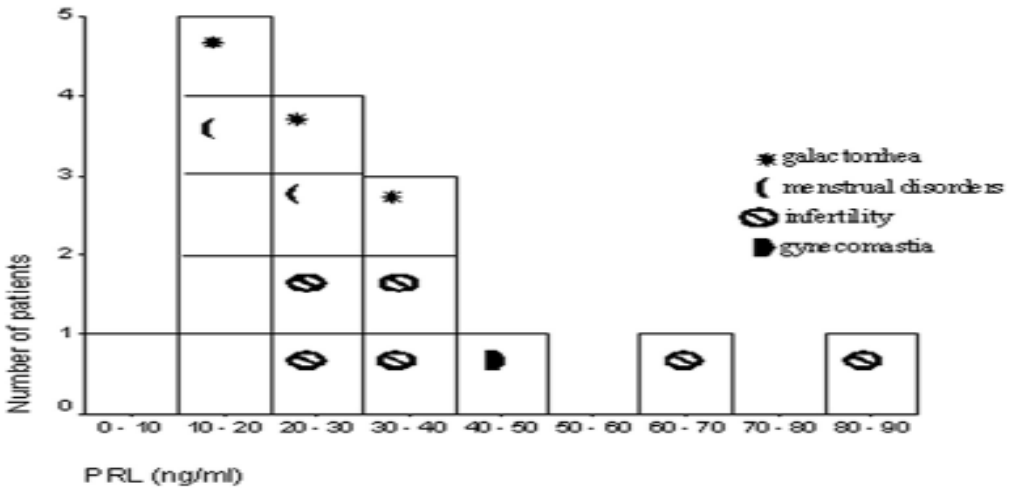

Figure 3. Clinical symptoms of macroprolactinemic patients (n=16).

than in systemic lupus erythematosus (17, 31), patients from A group or their relatives had no known autoimmune disorders. ATPO and antithyroglobulin antibodies were negative in all macroprolactinemic patients. In patients without macroprolactinemia, ATPO were present in 9 patients.

The relative differencies (RD)= (PRL Elecsys - PRL IRMA) / PRL Elecsys is higher in macroprolactinemic group than in true prolactinemic patients (0.53 + 0.29 vs 0.43 + 0.28, p=0.03 -Mann Whitney Test). PRL concentration in all three groups are shown in table 2. PRL determined by Elecsys was higher than PRL determined by IRMA, both in macroprolactinemic (A) and hyperprolactinemic (B) group. One of the patients with macroprolactinemia had PRL level 203 ng/ml with Elecsys and 10 ng/ml with IRMA. The difference between the two methods used (Δ = PRL determined by Elecsys - PRL determined by IRMA) correlated with big-big PRL level determined by CFG with Elecsys in all hyperprolactinemic patients. The strongest correlation was noticed in patients with macroprolactinemia (A group), r=0.82, p<0.01 as compared with B group, r=0.39, p<0.01 in B group (Fig. 4). This correlation was not seen in the control group C: r= -0.27, p>0.05.

Protein A precipitation test correlated significantly with GFC (r=0.67, p<0.01, Sn=75%, Sp=95,5%), suggesting that it can be used in the screening of patients with

macroprolactinemia. There were 5 false negative and 3 false positive patients with protein A precipitation test.

Neuroradiological examination (IRM and/or CT) was performed in all patients.

Table 2. PRL concentration in all studied groups with two different assays

	A group (Macro PRL)	**B group** (Other HPRL)	**C group** (Normal PRL)
Number of patients	16	62	6
PRL IRMA (ng/ml) mean +SD	29.8+20.7	39.01+41.7	11.4+2.7
min	8	3	7.9
max	82	198	15
PRL Elecsys (ng/ml) mean+SD	84.1+68.8	72.1+63.3	13.7+4.5
min	20	15	9
max	237	132	20

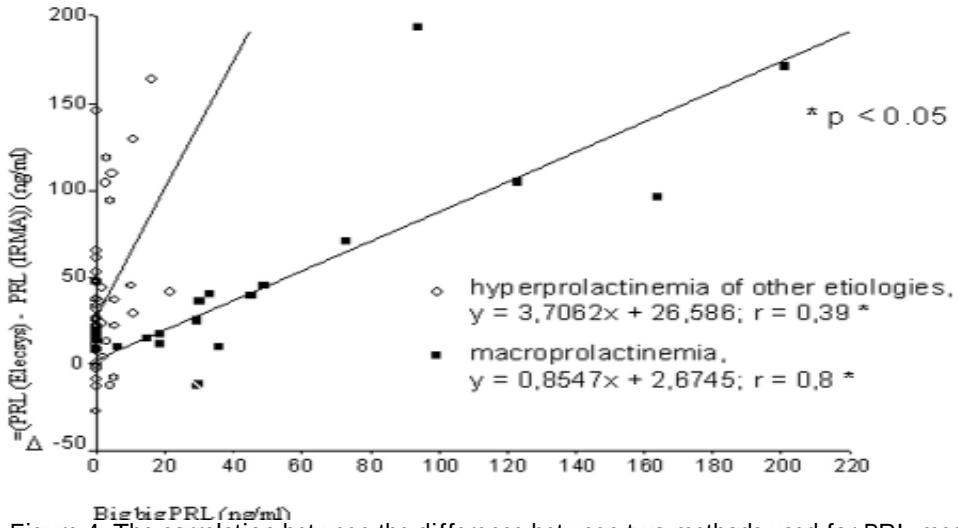

Figure 4. The correlation between the difference between two methods used for PRL measuring in hyperprolactinemic patients (n=78) with or without macroprolactinemia.

There was no patient with pituitary adenoma in macroprolactinemic group; some of the patients had heterogeneity of the pituitary and one had empty sella, similar to the patients in control group. In the B group, there were 8 patients with pituitary macroadenoma and 25 patients with microadenoma.

DISCUSSIONS

Macroprolactinemia, the predominance of high molecular weight variants of PRL, was discovered for many years in asymptomatic patients (32-35). Its clinical importance still remains an open problem. Although the first studies found macroprolactinemia in patients lacking the clinical features of hyperprolactinemia (36-40), many reported the presence of signs and symptoms (41-45), although less frequently. This suggests that macroprolactin has some biological activity *in vivo*. *In vitro*, macroprolactin has normal bioactivity, as it is proved by its mitogenic activity on Nb2 rat lymphoma cells (46). The difference between *in vitro* and *in vivo* biological activity was explained by the difficulties of high molecular prolactin to cross the capillary endothelium and to reach the target receptors (47, 48).

Macroprolactinemia determines hyperprolactinemia because of its low clearance (49), while in most cases pituitary lactotrophs have a normal capacity to secrete PRL. However, macroprolactin proved to be a heterogeneous molecule, and there are cases with macroprolactinemia and with high monomeric PRL levels of any cause.

In our study, 10 of 16 macroprolactinemic patients expressed some of the classical symptoms of hyperprolactinemia. Galactorrhea and infertility were not different in frequency from true hyperprolactinemic patients, and menstrual disorders were less frequent, similarly to normal prolactin patients. There were 4 patients with amenorrhea and macroprolactinemia, but 3 were postmenopausal, with elevated serum gonadotropins and 1 had hyperandrogenism, with normal gonadotropins level. So, in studied women with macroprolactinemia, amenorrhea could not be attributed to macroprolactinemia. Macroprolactinemia has clinical expression, but reduced compared with hyperprolactinemia with normal CFG.

Prolactin serum level in macroprolactinemia is usually less than 100 ng/ml, but there are cases with prolactin serum level higher than 200 ng/ml, which can lead to diagnostic errors, especially in the presence of pituitary incidentalomas (50). We had two patients with PRL level higher than 200 ng/ml, but fortunately without MRI evidence of pituitary adenoma. However, macroprolactinemia can be associated with any other cause of hyperprolactinemia, including prolactinoma (51). Pituitary imaging is necessary at least once in macroprolactinemic patients.

Macroprolactinemia determined a high variability of serum PRL. One patient with macroprolactinemia had 10 ng/ml PRL determined by IRMA and 203 ng/ml determined by Elecsys. This great variability has been explained by the capacity of IgG component of macroprolactin to mask PRL epitopes recognized by commercial assays (52, 53). In studied patients with hyperprolactinemia, the difference between the two methods used for PRL determination (Elecsys, which is the most accurate to macroprolactinemia and IRMA) depended on big big PRL level, as measured by CFG with Elecsys, with the strongest correlation seen in macroprolactinemic group. So, the level of PRL can be confusing without knowing the sensitivity to macroprolactin of the commercial test used to determine PRL level. The hyperprolactinemic group with

normal CFG also showed different values of PRL with both methods, so the difference between the two methods utilized for PRL determination cannot be used for detecting macroprolactinemia, as also shown by others (54).

CONCLUSIONS

Macroprolactinemia, the predominance of high molecular weight variant of PRL, shows a modest clinical manifestation. In macroprolactinemia, serum PRL level showed a great variability, which can be confusing if we do not use methods for macroprolactin determination. For a good clinical interpretation, the practitioner should know the sensitivity of each particular PRL assay to the presence of macroprolactin.

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