0013-7227/02/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 87(2):581–588

Macroprolactinemia Revisited: A Study on 106 Patients

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The predominance of high molecular weight PRL, or macroprolactinemia, has long been known in hyperprolactinemic patients with maintained fertility. Among 1,106 consecutive patients investigated for hyperprolactinemia in our center over a 10-yr period, serum PRL chromatography was performed in 368 cases because of discordant clinical, biological, or neuroradiological findings. We prospectively studied the 106 patients with macroprolactinemia (96 women, 6 men, 4 children) and compared them with the 262 hyperprolactinemic patients with a normal PRL elution pattern. We concluded the following: 1) the incidence of macroprolactinemia in our hyperprolactinemic population was at least 10%; 2) despite preserved fertility with uneventful pregnancies, some of the usual symptoms of hyperprolactinemia were present; 3) mean PRL values were 61 ± 66 μg/liter (range, 20–663) and exceeded 100 μg/liter in 8.5% of patients; 4) PRL levels usually remained stable over time; 5) on dopaminergic therapy, PRL returned to normal in 21of 45 treated patients; 6) during follow-up of 7 pregnancies, PRL increased to supraphysiological levels in 5; and 7) pituitary magnetic resonance imaging was normal in 78% of patients or revealed diverse pituitary lesions, including adenomas (n = 5). A diagnostic method for macroprolactinemia should be available to all centers to avoid unnecessary hormonal or radiological investigations and treatments. (*J Clin Endocrinol Metab* 87: 581–588, 2002)

HYPERPROLACTINEMIA MOST COMMONLY results from physiologic or pathologic conditions that cause hypersecretion of PRL by lactotroph cells. Physiologic causes include pregnancy and lactation; pathologic hyperprolactinemia may result from a lactotroph adenoma or from several readily identifiable causes that may interfere with normal dopamine inhibition of PRL secretion, such as hypothalamic or pituitary tumors, D2 dopamine receptor antagonist drugs, or hypothyroidism. Nevertheless, despite an extensive clinical, hormonal, and neuroradiological workup, no cause can be found in some patients whose serum PRL concentration may notwithstanding remain elevated for many years (1). Such patients are often characterized as having so-called idiopathic hyperprolactinemia. A subset of such patients may harbor microprolactinomas that are left undetected by current imaging techniques. Some of them however present with another cause of hyperprolactinemia, described by Jackson *et al.* (2, 3) as macroprolactinemia. This condition corresponds to the predominance of high molecular mass circulating PRL forms that have been postulated to represent PRL complexed with anti-PRL immunoglobulins (4–9). Many of the patients reported to present with macroprolactinemia have been described as lacking clinical manifestations typical of the hyperprolactinemic syndrome, with the exception of galactorrhea (2, 10–16). In our experience, however, a significant number of patients did suffer from at least some of these symptoms. Similarly, although macroprolactinemia was classically considered as associated with normal pituitary magnetic resonance imaging (MRI) findings and with PRL levels below 200 μg/liter, we found a substantial number of patients who did not meet such criteria. Over the past two decades, scattered reports with detailed clinical data have described 1–20 cases of macroprolactinemia totaling hardly more than 100 patients. In the present paper, we report a prospective study of 106 consecutive macroprolactinemic patients investigated in a single center over a period of 10 yr to more accurately define the main features of this condition, and we compared this population to 262 hyperprolactinemic patients with a normal PRL pattern at chromatography.

Abbreviations: MCP, Metoclopramide; MRI, magnetic resonance imaging; PRLmono, monomeric PRL levels; TPO, antithyroperoxidase.

Patients and Methods

Patients

From September 1990 to August 1999, 1,106 patients, including 919 women, were investigated for hyperprolactinemia in the same endocrinology department. In this population, a molecular sieve chromatography was performed in 368 cases (33%) to investigate for possible macroprolactinemia because of one of the following reasons: 1) lack of the usual symptoms associated with hyperprolactinemia; 2) lack of any visible pituitary lesion at MRI; and 3) lack of normalization of PRL levels after dopamine agonist or surgical treatment in the absence of any visible postsurgical remnant.

Endocrine evaluation

Initial investigations included a complete history, physical examination, and determination of plasma creatinin levels, free T_4, TSH, LH, and FSH using commercial immunoassay kits. Thyroid peroxidase and thyroglobulin antibodies were determined by luminescence immunoassay. PRL levels were measured at baseline using the same immunoassay kit throughout the study period (Immunotech, Marseille, France). The sen-

sitivity of the assay was 0.5 μg/liter, and intra- and interassay coefficients were 2 and 7%, respectively. Normal values were 2–20 μg/liter in men, and 5–25 μg/liter in women. PRL levels were also determined 20 and 30 min after iv administration of 200 μg TRH (TRH test) and 20 and 30 min after an iv bolus of 2.5 mg metoclopramide (MCP test) on a separate day. Both tests were arbitrarily considered as positive when peak PRL values were increased by 100% or more from baseline concentrations. A GnRH stimulation test was performed using standard procedures. All blood samples were obtained from an antecubital vein and during the early follicular phase in the case of menstruating women. Plasma samples were centrifuged and stored at −20 C until assays or gel filtration were performed.

Molecular sieve chromatography

Plasma samples (1–1.5 ml) were fractionated on a 50- × 1-cm Ultrogel AcA 44 column (Sepracor/IBF SA, Villeneuve la Garenne, France) initially calibrated with blue dextran, ovalbumin, monomeric radioiodinated PRL, and cytochrome C, and equilibrated with PBS (pH 7.4) containing 0.1% BSA and 0.02% sodium azide. On a routine basis, 40 0.8-ml fractions were collected over 100 min, and odd-numbered fractions between no. 15 and no. 39 were assayed for PRL, *i.e.* a total of 13 fractions. Gel filtration consistently yielded three distinct peaks of PRL immunoreactivity that were designated using the commonly used terminology as big-big (fractions 15–23; molecular mass, >100 kDa), big (fractions 27–31; molecular mass, ~50 kDa), or monomeric PRL (fractions 33–39; molecular mass, 23–25 kDa). The patients were considered to have macroprolactinemia when more than 50% of PRL immunoreactivity was eluted in the big or big-big fractions. In an attempt to extrapolate circulating PRL levels of monomeric hormone, we calculated extrapolated monomeric PRL levels (PRLmono) by multiplying total PRL concentrations and the percentage of monomeric hormone yielded by the chromatographic profile. For methodological reasons, these values cannot be viewed as accurate determinations and were only considered as an index. Gel filtration was also performed on the culture medium of two mixed PRL- and GH-secreting pituitary adenomas that were surgically removed and maintained in primary culture on an extracellular matrix as described elsewhere (17).

Neuroradiological examination

Pituitary MRI was performed in 81 of 106 macroprolactinemic patients, using precontrast coronal spin echo T1-weighed images, followed by postgadolinium T1-weighed imaging. The T1-weighed sequences provided reformatted images in the coronal plane, the oblique plane oriented along the pituitary stalk, and the axial plane oriented along the sellar floor.

Statistical analysis

For quantitative parameters, both groups were compared using *t* test. A significant threshold of 0.05 was chosen for *P* values. Qualitative parameters were compared using a χ^2 test or, when required by sample size, by means of Fisher's exact test. All statistical calculations were performed using the SPSS software (SPSS, Inc., Chicago, IL). Data are presented when appropriate as mean ± SD.

Results

Clinical status

The total hyperprolactinemic population studied (n = 1,106) included 61% patients with a PRL-secreting adenoma (Table 1). Of the 368 patients selected for a chromatographic study of circulating PRL on the basis of precise criteria as detailed in *Patients and Methods*, 106 (29%) had macroprolactinemia. This represented 10% (106 of 1,106) of the total population investigated. The patients who had a normal chromatographic profile and no other identifiable cause of hyperprolactinemia were classified as idiopathic hyperprolactinemias and represented 9% (102 of 1,106) of our hyperprolactinemic population (Table 1).

The 106 patients with macroprolactinemia were 96 adult women, 6 men, and 4 children. The main symptoms that were present at first diagnosis of hyperprolactinemia in the macroprolactinemic patients and in patients who had a normal chromatographic profile are summarized in Table 2.

Among the 37 macroprolactinemic adult women with menstrual disorders (including amenorrhea), 10 (aged 42–62 yr) had perimenopausal gonadotropin levels, 2 women below age 45 yr with normal gonadotropin levels were amenorrheic, and the remaining 25 had oligospaniomenorrhea, including 3 who had clinical, hormonal, and/or ultrasonographic features of the polycystic ovary syndrome. Thus, 24 of 96 women (25%) had menstrual disorders that may be attributed to macroprolactinemia. In comparison with the patients who had hyperprolactinemia and normal PRL chromatography, among the 127 of 259 women with menstrual disorders, 26 had perimenopausal gonadotropin levels, and a polycystic ovary syndrome was diagnosed in 6. Thus, 95 of 259 (37%) had menstrual disorders associated with hyperprolactinemia. In conclusion, menstrual disorders were significantly less frequent when hyperprolactinemia was associated with macroprolactinemia ($P = 0.03$).

A galactorrhea was present in 46% of the macroprolactinemic adult women (n = 44 of 96). Noteworthy, galactorrhea

TABLE 1. Main diagnostic categories in the total hyperprolactinemic population prospectively studied in our center over a 10-yr period

	Macroprolactinemia n = 106	Normal chromatography n = 262	Chromatography not done n = 738	Total n = 1,106
Prolactinomas	2 (2%)	89 (34%)[a]	580 (78%)	671 (60%)
Pituitary lesions[b]	16 (15%)	9 (3%)	108 (15%)	133 (12%)
Drug-induced	0	30 (11%)	22 (3%)	52 (5%)
Other causes[c]	3 (3%)	32 (12%)	28 (4%)	63 (6%)
Idiopathic	0	102 (40%)	0	102 (9%)
Isolated macroPRL	85 (80%)	0		85 (8%)

[a] Among the 255 hyperprolactinemic patients with normal chromatographic profile investigated by MRI, 70 had a prolactinoma associated with a visible pituitary lesion, and 19 patients were considered likely to harbor a microprolactinoma on the basis of symptomatic hyperprolactinemia with a negative response to both TRH and MCP tests, although pituitary MRI examination was normal. That is the reason why a chromatographic profile was obtained in these patients.

[b] Other adenomas (including mixed GH-PRL adenomas), intrasellar arachnoidoceles, intrasellar cysts, inflammatory lesions, stalk compression or interruption by various tumors. In the case of macroprolactinemia, a partial arachnoidocele (n = 8) or a small intrasellar cyst (n = 5) and a pure GH-secreting microadenoma (n = 1) were observed, but cannot be considered as the likely causes of hyperprolactinemia when macroPRL is present. In contrast, in two cases of mixed GH-PRL adenomas, hyperprolactinemia could be explained by both macroprolactinemia and adenomatous hypersecretion.

[c] Polycystic ovary syndrome, hypothyroidism, chronic renal failure, or hepatic failure.

TABLE 2. Comparison of clinical, biological, and neuroradiological findings between macroprolactinemic and hyperprolactinemic patients with normal PRL chromatography

	Macroprolactinemia n = 106	Normal chromatography n = 262	Statistical comparison
Sex ratio (F/M)	16/1	87/1	NS
Age (yr)	35.0 ± 11.1	32.8 ± 9.5	NS
Galactorrhea[a]	46%	66%	$P = 0.003$
Menstrual disorders[a]	39%	49%	$P = 0.04$
Galactorrhea + menstrual disorders[a]	12%	34%	$P = 0.003$
Fertility	68%[b]	70%	NS
Basal PRL (μg/liter)	61.4 ± 66.3	45.2 ± 29.8	NS
Positive response to TRH[c]	63%	58%	NS
Positive response to MCP[c]	88%	64%	$P = 0.0001$
Positive response to both tests[c]	59%	53%	NS
Negative response to both tests[c]	8%	36%	$P = 0.0001$
Normal MRI	78%	69%[d]	NS
Normalization on dopaminergic treatment	47%	65%	NS

F, Female; M, male.

[a] The total percentage of patients with galactorrhea or menstrual disorders is indicated in each group, including the patients who had both symptoms (the latter detailed on line 3).

[b] Fertility was evaluated in the 96 women over 18 yr.

[c] TRH and MCP tests were arbitrarily considered as positive when peak PRL values were increased by 100% or more from baseline concentrations.

[d] Among the 255 investigated by MRI, 176 had a normal MRI (69%).

was significantly less frequently associated with menstrual disorders in the macroprolactinemic patients compared with the hyperprolactinemic patients with a normal PRL chromatography (12 *vs.* 34%; Table 2). In addition, 2 of 12 patients with both galactorrhea and oligospaniomenorrhea had a PRL-secreting adenoma and 4 were perimenopausal; therefore, in 6 of 96 adult women (6%), the galactorrhea-menstrual disorders syndrome seemed solely attributable to macroprolactinemia.

Among the 25 of 96 (29%) women in whom macroprolactinemia had been found as part of the diagnostic work-up for infertility, 56% had secondary infertility and had previously obtained 1–3 pregnancies. Finally, 65 of the 96 women over 18 yr of age (68%) had previously had 1–6 pregnancies, and only 2 of the 30 nulliparous women were over 40.

In male patients, three had erectile dysfunction and decreased libido, and three reported normal sexual function. All of them had normal T levels and normal gonadotropin response to a GnRH stimulation test.

As previously reported elsewhere (18), our series included four girls aged 4–12 yr discovered by routine PRL determinations as part of an endocrine work-up for precocious puberty (n = 2), frontal headaches, or short stature.

Initial PRL levels

Baseline PRL levels averaged 61.4 ± 66.3 μg/liter (extremes, 20–663), and 91% of them were below 100 μg/liter, most patients having PRL values ranging from 20–60 μg/liter as shown on Fig. 1. When the nine patients with PRL levels above 100 μg/liter were compared with the macroprolactinemic patients with PRL below 100 μg/liter, no statistical difference was found in terms of clinical presentation, and six of them had regular menses.

Chromatographic data

A macroprolactinemia elution pattern is presented on Fig. 2A. Of the 106 patients in whom high molecular mass PRL

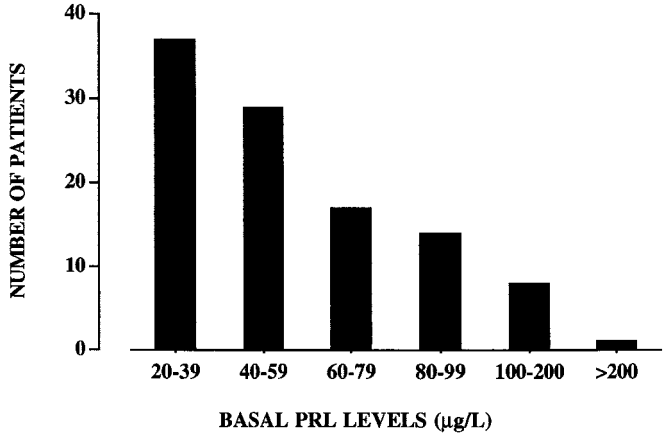

FIG. 1. Baseline PRL levels in our 106 macroprolactinemic patients: 97 of 106 patients presented with basal PRL below 100 μg/liter, and most patients (n = 66) had PRL values ranging from 20–60 μg/liter. When the nine patients with PRL levels above 100 μg/liter were compared with the macroprolactinemic patients with PRL below 100 μg/liter, no statistical difference was found in terms of clinical presentation, and six of them had regular menses.

represented at least 50% of circulating PRL forms, the vast majority (92%; n = 98) had predominant big-big PRL forms, representing 74.7 ± 14.6% (extremes, 29–99%) of PRL immunoreactivity in the gel filtration eluate. In these patients, big PRL and monomeric PRL accounted for 3.9 ± 6.6% (0–30%) and 21.4 ± 12.5% (1–49%), respectively, of total PRL immunoreactivity. In the remaining 8 patients, big PRL was the main PRL form, representing 54.1 ± 19% (34–85%) of eluted PRL, whereas big-big and monomeric PRL represented 14.7 ± 14.1% (0–31%) and 31.1 ± 12.9% (10–45%), respectively. No difference was found in terms of clinical or biological presentation, whether big-big or big PRL was the predominant size variant. No statistically significant correlation was present between total PRL concentrations and the percentage of big-big PRL determined by chromatography

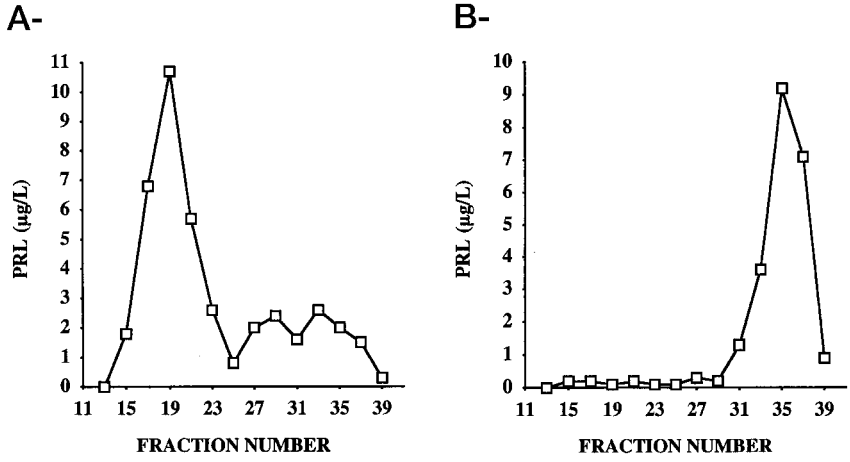

FIG. 2. A, Chromatographic elution pattern of 0.8 ml of serum drawn in patient (F,48) presented in Table 3 (PRL = 32 μg/liter). Gel filtration yielded three peaks of PRL immunoreactivity. In this case, the first peak corresponding to big-big PRL (fractions 15–23; molecular mass >100 kDa) represented 69% of total immunoreactive PRL; the second peak (15%) represented big PRL (fractions 27–31; ~50 kDa); and monomeric PRL (fractions 33–39; 23–25 kDa) was found in the third peak (16%). This was typical of macroprolactinemia, because more than 50% of PRL immunoreactivity was eluted in high molecular weight fractions. B, Chromatographic elution pattern of 0.8 ml of culture medium of the adenoma surgically removed in this patient. Virtually all of immunoreactive PRL released into the medium corresponded to monomeric PRL variants, and no big-big PRL could be detected.

(r = 0.22; P = 0.3). Extrapolated PRLmono, calculated as described in *Patients and Methods*, were within normal limits for total PRL on average (11.9 ± 11.7 μg/liter; extremes, 1–106) and exceeded 20 μg/liter only in 10 cases. One of these was a prolactinoma patient (PRLmono, 29 μg/liter). Such an extrapolated value did not appear as a good index of PRL bioactivity because 4 of the 10 patients with PRLmono above 20 μg/liter had regular menses, and 6 of 10 had galactorrhea. There was no significant difference between patients with PRLmono greater than 20 μg/liter and those with PRLmono less than 20 μg/liter in terms of frequency of clinical symptoms.

Dynamic tests

A positive response of PRL to TRH stimulation was found in 62 of the 98 macroprolactinemic patients investigated (63%), and a positive response to MCP was found in 67 of 76 patients (88%). Both tests had been performed in a total of 76 patients and were positive in 45 cases (59%) and negative in 6 cases (8%). Dissociated responses (positive MCP test and negative TRH test) were observed in 25 patients.

Autoimmunity

All patients had normal TSH and free thyroid hormone levels. Of the 36 patients tested for thyroid autoimmunity, 5 (14%) were positive for antithyroperoxidase (TPO) antibodies, including 3 positive for both TPO and antithyroglobulin antibodies. In hyperprolactinemic patients with normal chromatographic profile, 15% (12 of 78 tested) were positive for TPO antibodies.

Neuroradiological findings

Pituitary MRI was performed in 81 patients (76%). It was found normal in 63 of the cases (78%), revealed an intrasellar arachnoidocele in 8 patients (10%), a neuroradiological aspect compatible with a microadenoma in 3, a macroadenoma in 2, and an intrasellar pituitary cyst in 5 cases. These cystic lesions were found to remain stable after 2–6 yr of follow-up; all of the five suspected adenomas were removed by transsphenoidal surgery. Immunohistochemistry revealed two pure prolactinomas, two mixed PRL- and GH-secreting adenomas, and one pure GH-secreting adenoma. Clinical and biological presentation of these patients is represented in Table 3.

Interestingly, as illustrated on Fig. 2B, the gel filtration pattern of the culture medium of the adenoma surgically removed from the two acromegalic patients who had a mixed GH- and PRL-secreting adenoma and a pure GH adenoma (presented in Table 3 as F, 48 and M, 30) yielded a single immunoactive PRL peak of monomeric hormone, in contrast with the typical macroprolactinemic pattern obtained in plasma [percentage big-big and big PRL, 69 and 15% (Fig. 2A); 60 and 20%, respectively]. This finding strongly suggested that the big-big circulating PRL complex was not secreted by the lactotrophs but rather was of peripheral origin, *i.e.* formed within the vascular compartment.

Follow-up

A long-term follow-up (≥2 yr) could be obtained in 42 patients of the present series, including 23 who were followed for 5 yr or more. On average, PRL concentrations remained grossly stable over the follow-up period, as shown on Fig. 3. On an individual basis, however, very large variations were sometimes observed (apart from pregnancies or dopamine agonist therapies), reaching a more than 5-fold amplitude in 13 cases. We did not observe a consistent gradual decrease or increase over time of basal PRL levels in any of our cases.

On dopamine agonist therapy administered over 16.3 ± 15.1 months (1–48 months), 21 of 45 treated patients normalized their PRL levels (20 on bromocriptine at doses ranging from 2.5–15 mg/d and 1 on quinagolide at doses from

TABLE 3. Clinical and biological presentation of the 5 patients who presented with macroprolactinemia associated with a pituitary adenoma

Patient	Clinical features	Basal PRL (μg/liter)		Basal GH[a] IGF1 (μg/liter)		Big Big PRL Big PRL (%)	IHC
		preop	postop	preop	postop		
F, 22	Galactorrhea, regular menses, frontal headaches	44	34	N	N	65	Prolactinoma
				N	N	0	
F, 45	Menstrual disorders, frontal headaches	84	31	N	N	89	Prolactinoma
				N	N	0	
F, 48	Acromegaly, menstrual disorders, galactorrhea	32	32–56	80	N	69	Mixed PRL- and GH-secreting adenoma
				830	N	15	
F, 43	Acromegaly, regular menses	32	30–40	50	N	0	Mixed PRL- and GH-secreting adenoma
				580	N	85	
M, 30	Acromegaly, decreased libido, frontal headaches	27	22–27	30	N	60	GH-secreting adenoma
				670	N	20	

Basal PRL, GH, and IGF-I values (μg/liter) are indicated before (preop) and after (postop) surgery.

[a] Mean of eight hourly samplings.

N, Normal GH (<6 μg/liter) and IGF-I values (μg/liter) for age (adult, 107–310; children 0–4 yr, 49–171; >4 yr, 76–499; Tanner's pubertal stage P2, 247–396; P3, 249–642; P4, 271–550); IHC, immunohistochemical diagnosis.

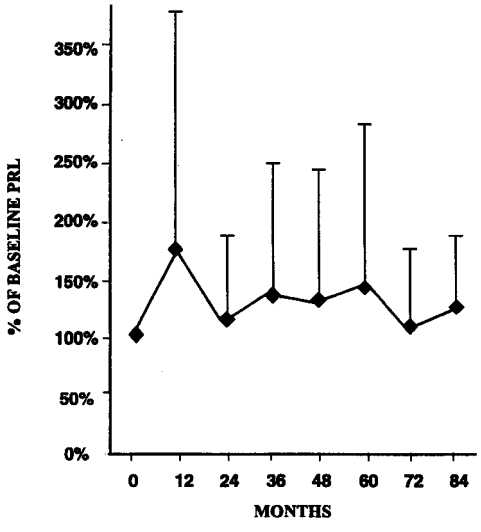

FIG. 3. Long-term follow-up of PRL levels in 42 macroprolactinemic patients. PRL levels are expressed as a percentage of the initial value (100%). They remained stable over the follow-up period (2–7 yr). On an individual basis, as evidenced by SD bars, very large variations were observed.

0.075–0.15 mg/d). One of the dysovulatory women who had isolated galactorrhea and regular menses could obtain a pregnancy only after bromocriptine therapy. The female patient with the highest baseline PRL levels (660 μg/liter) attained normal PRL values (12 μg/liter) on 5 mg/d bromocriptine, allowing resumption of regular ovulatory cycles that had otherwise never been observed in this case.

A total of seven women with macroprolactinemia were followed during pregnancy. All seven pregnancies and deliveries were uneventful. In most cases, macroprolactinemia was diagnosed after delivery, although hyperprolactinemia had been known before pregnancy, and in two cases was preceded by dopamine agonist treatment. As detailed in Table 4, PRL levels remained stable throughout pregnancy in two cases, and increased above normal pregnancy values in the other five cases at the end of the first trimester. This finding led to bromocriptine therapy in all cases, that allowed to stabilize PRL values.

Discussion

In the present study, we describe the main clinical and biological features of 106 patients with macroprolactinemia investigated in the same endocrinology department over a period of 10 yr. In our series, characterized by a high proportion of pituitary tumors because of our close collaboration with a department of neurosurgery, macroprolactinemia represented 10% of our hyperprolactinemic patients (106 of 1,106), although only 368 of them had a chromatographic profile performed. In the general population, the incidence of macroprolactinemia has previously been estimated around 0.1–0.2% (10, 19, 20). Moreover, among sera examined in endocrinology laboratories, as many as 20–30% of the hyperprolactinemic samples were found to have macroprolactinemia (10, 19, 21–24). These data suggest that this condition represents an often overlooked diagnosis and a cause of hyperprolactinemia whose frequency is certainly underestimated.

We selected for chromatography all patients displaying discrepant clinical, biological, or follow-up data. More precisely, as previously detailed, this included the following distinct settings: 1) hyperprolactinemia without gonadal dysfunction; 2) cases that would otherwise have been labeled idiopathic hyperprolactinemia, because no other identifiable cause of elevated PRL could be evidenced; and 3) lack of normalization of PRL despite appropriate medical or surgical treatment, as previously suggested (9). Other reasons for performing a chromatographic study of circulating PRL are the finding of a marked discrepancy between different PRL values obtained in the same patient using distinct immunoassay methods, as underlined by several authors (4, 19, 21), or absence of normalization of PRL levels after discontinuation of a drug known to increase PRL concentration (9). Noteworthy, despite the relatively high frequency of macroprolactinemia, chromatography of PRL seems to be neither a commonly requested nor even a widely available investigation method, a limitation that may partly be due to the cost and duration of the chromatographic technique. This prompted several laboratories to develop nonchromatographic screening methods, mainly the polyethylene glycol precipitation assay (9, 19, 22, 23, 25–27). These methods are

TABLE 4. Follow-up of PRL levels during pregnancy in seven women

	Before pregnancy	T1	T2	T3
Stable PRL (μg/liter) (n = 2)	65.5	65.0	65.0	95.0
Increased PRL (μg/liter) (n = 5)	41.6 ± 11.6	312.7 ± 96.6	394.7 ± 38.3	530.5 ± 43.1
Total PRL (μg/liter) (n = 7)	48.4 ± 23.1	213.6 ± 153.9	262.8 ± 184.3	312.8 ± 252.7

PRL levels are presented as the mean or mean ± SD determined during each trimester (T1–T3).

based on the assumption that macroprolactinemia is mainly due to the presence of circulating anti-PRL antibodies, probably IgG, as corroborated by many pieces of evidence (4, 6, 7, 9, 28, 29). Our observations of a normal PRL elution pattern in the culture media of two pituitary adenomas removed from patients with macroprolactinemia suggested the peripheral nature of this disorder. The mechanisms that trigger production of such antibodies remain to be elucidated.

Macroprolactinemia may be observed in both sexes (9–11, 21, 30–34), although women represent 89% of published cases, and at all ages, including subjects over 65 yr (6, 29, 34) and below 12 yr (18, 31, 35). This condition has been recognized for many years in asymptomatic patients or research volunteers (2, 13–15, 31, 33, 34). In more recent series, however, as well as in ours, a significant proportion of patients with macroprolactinemia appeared to suffer from symptoms commonly associated with hyperprolactinemia. Indeed, in our experience, circumstances leading to the diagnosis of macroprolactinemia included menstrual disorders (39%), infertility (29%), and galactorrhea (46%). Among the 107 women described in previously published series (2, 3, 5, 6, 9, 12–16, 28, 29, 32, 36–43), the classical symptoms of hyperprolactinemia were similarly observed (menstrual disorders, 28%; infertility, 34%; galactorrhea, 42%). In 52 cases evaluable in terms of pregnancies (8, 13, 15, 16, 21, 28, 32, 37–39, 43), fertility was maintained in 81%, as it was in the majority of our population (68%). In men, despite alleged sexual dysfunction that generally represented the reason for PRL determination, gonadotroph function was preserved, as previously observed (11, 30). Together, these findings favor the idea of a weak *in vivo* biological activity for macroprolactin. This is unlikely to be due to a reduced biological activity of this PRL variant because big-big PRL fractions have been shown in several studies to have normal bioactivity in the NB2 bioassay (12, 29, 30, 33). A decreased bioavailability of PRL appears as a more likely explanation for this finding because big-big PRL complexes may indeed escape more slowly from the capillaries (12) as indirectly corroborated by clearance studies (29, 32).

Macroprolactinemia may be associated with any other cause of hyperprolactinemia. Whether such associations are coincidental remains a matter of debate. Such conditions obviously may have drawn medical attention on macroprolactinemia that would otherwise remain undiagnosed. More specifically, some authors have suggested an increased incidence of autoimmune thyroid disorders in macroprolactinemia (8, 39). This finding was not confirmed by our data, because only one of our patients had overt autoimmune hypothyroidism, and 14% of the patients tested had detectable TPO antibodies, a proportion that did not differ from that found in hyperprolactinemic patients with a normal chromatographic profile and in a normal population (44). Association with a pituitary adenoma deserves particular attention. The very first cases of hyperprolactinemia attributable to predominant high molecular mass PRL forms were actually described in acromegalic patients who were shown to be devoid of high molecular mass GH forms in excess (45, 46), as in our two cases (data not shown). In two other studies, three patients had radiological evidence of a microadenoma at pituitary computerized tomography scanning, but no histological confirmation was provided (5, 37), and only one previous report had mentioned a surgically proven microadenoma in a macroprolactinemic patient (9). We observed five cases of histologically confirmed pituitary adenomas in patients with macroprolactinemia. The possible association of macroprolactinemia with a pituitary tumor or other causes of hyperprolactinemia warrants a cautious initial and subsequent work-up of patients with this disorder and clearly does not allow us to limit this diagnosis to the sole field of idiopathic hyperprolactinemia.

From a clinical viewpoint, another important issue is the level of hyperprolactinemia attained under different circumstances. It is classically considered that basal PRL levels exceeding 200–500 μg/liter can be associated with nothing but a macroprolactinoma (47) and that patients with macroprolactinemia, in contrast, have only modest hyperprolactinemia. However, in view of observations from our group and others, such an assumption cannot be taken as a rule. In 8.5% of our patients and in 28 of 137 other published cases, baseline PRL concentration was above 100 μg/liter, reaching values as high as 1,232 μg/liter (3, 6, 7, 12, 29, 31, 34, 36, 40, 43, 48). During pharmacological testing, a preferential increase of the monomeric PRL form has been demonstrated by several authors (9, 16, 32, 43). Resultant variations in serum make it difficult to rely on provocative tests in the interpretation of high PRL levels in the context of macroprolactinemia. This is well illustrated by our data because all patterns of responses were observed after TRH or MCP. In our experience, however, a negative response to stimulation tests, especially to the MCP test, remained indicative of adenomatous hyperprolactinemia even in this setting (as shown in Table 2). On dopamine agonist therapy, monomeric PRL has been shown to preferentially decrease (15, 16), and normalization of PRL levels was observed in many cases (12, 14, 15), as in 47% of our patients. This sometimes appeared to allow obtention of a pregnancy and alleviation of symptoms (28). Systematic abstention from any medical treatment in macroprolactinemia may thus be questionable in individual cases. In some patients, as observed by others, macroprolactinemia may present as pseudoresistance to dopaminergic

therapy, because PRL levels may fail to normalize on such a treatment (5, 6, 9, 28). True resistance to dopamine agonists on the contrary has been shown to be characterized by a decreased sensitivity to dopamine at the level of lactotroph cells (49, 50). During pregnancy, our observations as well as previously published cases show that an exaggerated elevation of PRL levels may be observed at first trimester, that this condition does not seem to affect fetal or maternal outcomes, and that postpartum PRL levels usually return to prepregnancy values (9, 28, 51). On long-term follow-up, PRL levels have been shown in a single report on two patients to decrease after 5 yr (39). In keeping with our findings, PRL levels as well as PRL autoantibody titers have been shown by other authors to remain stable over time (28). How long PRL levels should be monitored in these patients currently remains an open question.

The large series reported here allows us to draw several clinically relevant conclusions: 1) macroprolactinemia represents a major, and often overlooked, cause of hyperprolactinemia; 2) it should be sought in hyperprolactinemic patients whenever discrepant findings are observed in terms of clinical presentation or biological follow-up; 3) despite preserved fertility with uneventful pregnancies, some of the usual symptoms of hyperprolactinemia may be present; 4) although usually modestly elevated, PRL levels may occasionally be well over 100 μg/liter; 5) PRL levels most often remain stable over time; 6) dopaminergic treatment may sometimes be beneficial, but does not always allow normalization of PRL concentration; and 7) a pituitary lesion such as a prolactinoma may be associated and should be ruled out by neuroradiological imaging. Making a diagnosis of macroprolactinemia however avoids repeat hormonal or radiological investigations and unnecessary treatments. A routine diagnostic method for this biological disorder should thus be available to all specialized investigation centers.

Acknowledgments

We are indebted to all clinicians who referred patients to our center, to Dr. Enzo Caruso and Dr. Emanuela Rossi for their help in the development of the chromatographic procedures and adenoma cell culture studies, to Dr. Sylvie Romain and Henriette Gerard for performing routine chromatographic studies, and to Dr. Véronique Garcia-Jarrige for fruitful discussions.

Received March 12, 2001. Accepted November 8, 2001.

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