The importance of routine screening for macroprolactin in symptomatic patients with idiopathic hyperprolactinemia

A importância do rastreamento de rotina da macroprolactina em pacientes sintomáticas com hiperprolactinemia idiopática

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ABSTRACT

Objective: *To evaluate the importance of screening for macroprolactin in symptomatic patients with apparent idiopathic hyperprolactinemia.* ***Methods:*** *During 20 months, the prevalence of macroprolactinemia was evaluated among consecutive symptomatic female patients with apparent idiopathic hyperprolactinemia routinely followed in two neuroendocrinology reference centers from Recife. This prevalence has never been systematically evaluated.* ***Results:*** *A total of 82 patients (mean age, 36.1±7.3 yrs; age range, from 25 to 50) were included; 69 of them (84.1%) had been treated with cabergoline. The screening for macroprolactin was positive in 22 patients (26.8%), 15 of whom (68.2%) misleadingly received longterm treatment with cabergoline. The clinical and demographic features, as well as baseline prolactin levels, were comparable in patients with true idiopathic hyperprolactinemia and in those with macroprolactinemia.* ***Conclusion:*** *Macroprolactinemia was found in about one quarter of the patients with apparent idiopathic hyperprolactinemia. Our findings highlight the importance of routine screening for macroprolactin in all patients with idiopathic hyperprolactinemia, regardless their clinical features, in order to avoid misdiagnosis and unnecessary treatment with dopamine agonists.*

Keywords: *Macroprolactin. Screening. Macroprolactinemia. Idiopathic hyperprolactinemia.*

RESUMO

Objetivo: Avaliar a importância do rastreamento de rotina de macroprolactina em mulheres sintomáticas com aparente hiperprolactinemia idiopática. **Métodos:** Durante 20 meses, a prevalência de macroprolactinemia foi avaliada entre pacientes sintomáticas com aparente hiperprolactinemia idiopática rotineiramente seguidas em dois centros de referência de neuroendocrinologia de Recife. Esta prevalência nunca fora sistematicamente avaliada. **Resultados:** Um total de 82 mulheres (média das idades, 36,1 ± 7,3 anos, faixa etária de 25 a 50) foram incluídas; 69 delas (84,1%) foram tratadas com cabergolina. A pesquisa para macroprolactina se mostrou positiva em 22 pacientes (26,8%), 15 das quais (68,2%) equivocadamente foram tratadas a longo prazo com cabergolina. As características clínicas e demográficas, bem como os níveis basais de prolactina, foram comparáveis em pacientes com hiperprolactinemia idiopática verdadeira e naquelas com macroprolactinemia. **Conclusão:** Macroprolactinemia foi encontrada em cerca de um quarto das pacientes com aparente hiperprolactinemia idiopática. Os resultados destacam a importância da pesquisa de rotina para macroprolactina em todas as pacientes com hiperprolactinemia idiopática, independentemente de suas características clínicas, a fim de se evitar diagnóstico incorreto e tratamento desnecessário com agonistas dopaminérgicos.

Palavras-chave: Macroprolactina. Pesquisa. Macroprolactinemia. Hiperprolactinemia idiopática.

INTRODUCTION

Hyperprolactinemia is the most common endocrine disorder of the hypothalamic-pituitary axis[1,2]. Idiopathic hyperprolactinemia is the presence of elevated serum prolactin (PRL) levels in a patient in the absence of demonstrable pituitary or central nervous system disease and of any other recognized cause of increased PRL secretion[1,3,4]

PRL size is heterogeneous in terms of circulating molecular forms. The predominant form in healthy subjects and in patients with prolactinomas is monomeric PRL (molecular weight of 23 kDa), while dimeric (4560 kDa), and macroprolactin (150170 kDa) correspond to less than 20% of the total PRL[5,6]. When the patient

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serum of hyperprolactinemia contains mostly macroprolactin, the condition is macroprolactinemia[1,7]. In approximately 90% of cases, macroprolactin is composed of a complex formed by an IgG and a monomeric PRL[1,8]. Macroprolactin causes hyperprolactinemia as a consequence of low renal PRL clearance and decreased stimulation of the dopaminergic tonus[8]. Due to its high molecular mass, macroprolactin has both low biological activity and low bioavailability[8,9], thus explaining why most patients with macroprolactinemia lack typical symptoms related to hyperprolactinemia[8,11]. Therefore, macroprolactinemic patients do not need to be treated[10,12], unlike those with idiopathic hyperprolactinemia[3].

The screening for macroprolactin has been considered for asymptomatic patients[2,3,8,12]. But, the presence of galactorrhea, menstrual disorders or erectile dysfunction do not exclude such diagnosis, as shown in many clinical studies[10-16]. This finding could be explained by the concomitance of macroprolactinemia with other disorders, such as polycystic ovary syndrome non-functioning pituitary adenomas, prolactinomas or any other causes of monomeric hyperprolactinemia [1,10,15-17].

The authors aimed to, prospectively, determine during a period of 20 months, the prevalence of macroprolactinemia among symptomatic female patients with apparent idiopathic hyperprolactinemia, which has never been systematically evaluated. Misdiagnosis in these cases could lead to unnecessary treatment with dopamine agonists.

METHODS

The research was performed in two neuroendocrinology centers from Recife, Brazil (Endocrine Research Center of Pernambuco and Division of Endocrinology of Hospital das Clínicas, Federal University of Pernambuco). It was also compared clinical, laboratorial and demographic features in patients with or without macroprolactinemia.

PRL was measured by chemiluminescence immunoassay (Diagnostic Products Corporation, Immulite 2000®). The reference range was 2.8 to 29.2 ng/mL. Macroprolactin was determined by measuring the serum PRL level before and after polyethylene glycol (PEG) precipitation. As suggested by Vieira et al.[18], PRL recoveries of < 40% and > 60% after PEG precipitation were used as the criteria diagnosis for macroprolactinemia and monomeric hyperprolactinemia, respectively.

Results were expressed as percentages or mean values ± SD, unless otherwise stated. For comparison of categorical variables, the chi-squared test or the Fisher exact test were used when appropriate. A paired Student's t-test was performed for the comparative analysis of two means A p-value < 0,05 was considered statistically significant.

The study was approved by local Ethics and Scientific Committees and all patients gave written informed consent.

RESULTS

A total of 82 patients (mean age, 36.1 ± 7.3 yrs; age range, 2550) were included in the study; 69 of them (84.1%) had been treated with cabergoline.

The screening for macroprolactin was positive in 22 patients (26.8%), 15 of whom (68.2%) received long-term treatment with cabergoline.

The clinical and demographic features were comparable in patients with true idiopathic hyperprolactinemia and in those with macroprolactinemia (Table 1). However, the rate of patients experiencing both menstrual disorders (oligomenorrhea or amenorrhea) and galactorrhea was significantly higher in idiopathic hyperprolactinemia group (33.3% vs. 9.1%; p = 0.02). In contrast, the rates of patients whose presenting symptoms were isolated galactorrhea or isolated menstrual disorders were similar in both groups (Table 1 and Figure 1).

Table 1. Comparison of clinical, demographic and laboratorial features at diagnosis in symptomatic female patients with macroprolactinemia or idiopathic hyperprolactinemia

Features	Macroprolactinemia (n=22)	Idiopathic hyperprolactinemia (n=60)	p-value
Age (years)	37.3 ± 9.65	35.7 ± 6.51	0.11
Mean PRL levels (ng/mL)	137.05 ± 72.12 (range, 70 - 295)	156.45 ± 65.07 (range, 75 - 286)	0.15
Rate of isolated galactorrhea (%)	22.7 (n=5)	10 (n=6)	0.13
Rate of isolated menstrual disorders (%)	68.2 (n=1 5)	56.7 (n=34)	0.24
Rate of both menstrual disorders and galactorrhea (%)	9.1 (n=2)	33.3 (n=20)	0.02
Rate of PRL normalization during CAB treatment (%)	40 (n= 6/15)	81.4 (n= 44/55)	<0.0 1

CAB: cabergoline; PRL: prolactin

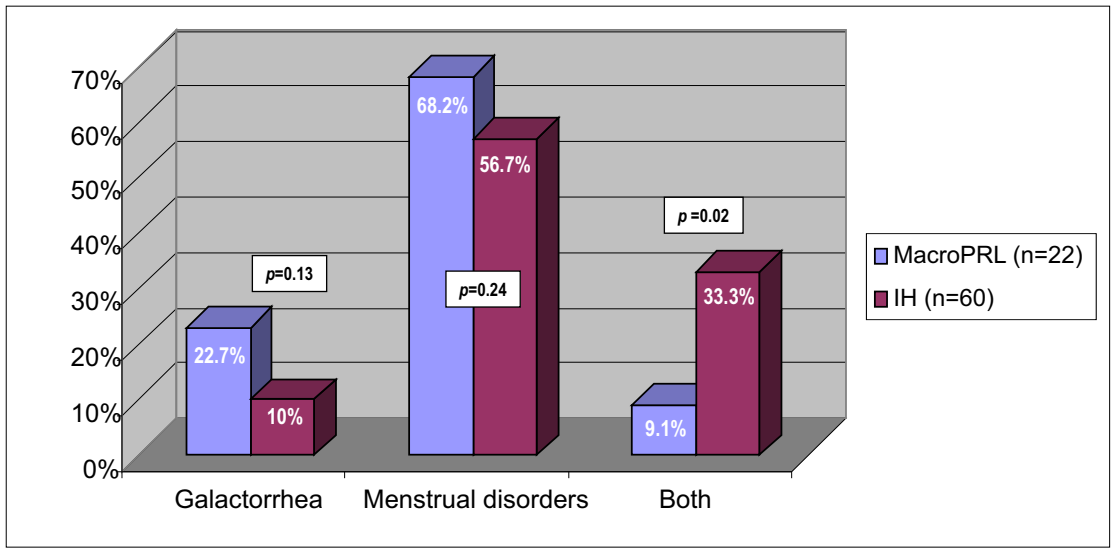

Figure 1. Presenting clinical features of female patients with macroprolactinemia (MacroPRL) or idiopathic hyperprolactinemia (IH). The combination of galactorrhea and menstrual disorders was sigifinificantly lower in macroPRL group than among IH patients (9.1% vs 33.3%, p = 0.02).

As shown in Table 1, PRL levels did not significantly differ in patients with macroprolactinemia (range, 70.295 ng/mL; mean, 137.0572.12) and in those with true idiopathic hyperprolactinemia (range, 75.286 ng/mL; mean, 156.45 ± 65.07; p = 0,15). However, PRL levels < 100ng/mL were more frequent in the macroprolactinemia group (Figure 2). After PEG precipitation, all patients with macroprolactinemia had monomeric PRL levels within the normal range.

During cabergoline treatment, PRL normalization was achieved in 40% of patients with macroprolactinemia and in 81.4% of those with true idiopathic hyperprolactinemia (p < 0.01) (Table 1).

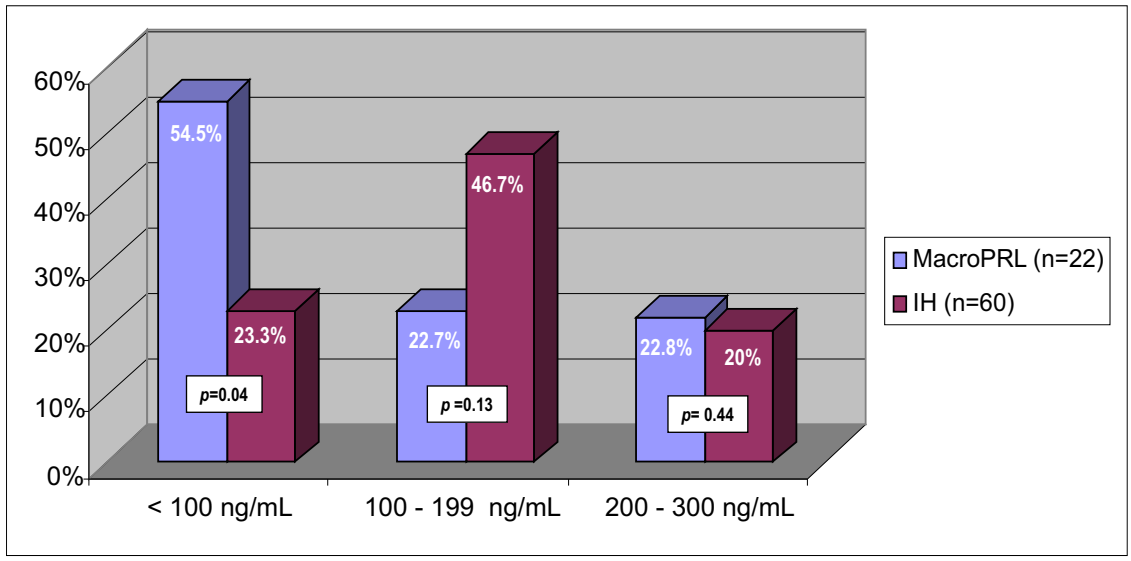

Figure 2. Distribution of patients with macroprolactinemia (MacroPRL) or idiopathic hyperprolactinemia (IH) according to their baseline prolactin (PRL) levels. Mean PRL levels were similar in both groups (p = 0,15).

DISCUSSION

In this prospective study, the screening for macroprolactin was positive in 26.8% of 82 symptomatic female patients with a previous diagnosis of idiopathic hyperprolactinemia. In two other studies, the prevalence of macroprolactinemia in subjects with idiopathic hyperprolactinemia ranged from 34.2% to 68.3% but the clinical profile of the patients was not mentionned[16,19].

Macroprolactinemia has been recognized for many years in asymptomatic patients or research volunteers[1,5,6]. Macroprolactin was subsequently shown to display low bioactivity and low bioavailability[8,9], which would explain why most patients lack symptoms related to hyperprolactinemia[10-15]. Accordingly, the 2011 Endocrine Society guidelines suggest screening for macroprolactin only in the investigation of asymptomatic hyperprolactinemic subjects[2]. However, as shown in more recent series, galactorrhea and hypogonadism symptoms (oligo/amenorrhea, infertility and erectile dysfunction) may be often found in patients with macroprolactinemia[10-15,19,20].

Among 64 macroprolactinemic patients, we previously demonstrated that 36 subjects (56.3%) were asymptomatic while the remaining presented with hypogonadism symptoms and/or galactorrhea[20]. In contrast, only 11.5% of subjects with monomeric hyperprolactinemia were asymptomatic ($p < 0.001$). There was no significant difference between both groups regarding the frequency of galactorrhea (12.9% vs 28.6%, $p = 0.690$), menstrual disturbances (24.1% vs 25.7%, $p = 0.834$), and erectile dysfunction (50% vs 42.3%, $p = 0.722$). Conversely, the combination of galactorrhea and menstrual disturbances was significantly more frequent in women with monomeric hyperprolactinemia (34.3% vs 1.8%, ($p< 0.001$)[20], similarly to the findings of the currrent study. Indeed, menstrual disorders or galactorrhea were equally prevalent in patients with or without macroprolactinemia, whereas the combination of these features largely predominates in the Idiopathic hyperprolactinemia group.

Our data are in agreement with those reported by other authors[11-16,19]. Overall, among macroprolactinemic women, menstrual disturbances were found in 12.4%, infertility in 4.9%, and galactorrhea in 1.8%[11-16,19]. In two studies, 50.7% of men with macroprolactinemia complained of erectile dysfunction[13,14].

All these findings are not surprising in that the symptoms that prompt measurement of PRL are nonspecific and may occur coincidentally in patients who present with hyperprolactinemia due to macroprolactin but also have associated disorders, such as idiopathic galactorrhea[21], chronic anovulation (eg, polycystic ovary

syndrome)[22], psychogenic erectile dysfunction[23] or non-functioning pituitary tumors[1,24]. Moreover, macroprolactinemic patients may also have the concomitance of prolactinomas or any other causes of monomeric hyperprolactinemia [1,16,19]. In this setting, PRL levels will be above the normal range after PEG precipitation[1,8].

Idiopathic hyperprolactinemia is thought to mostly result from very small prolactinomas that can escape detection by magnetic resonance imaging[1-4]. An autoimmune mechanism could also be involved in some cases[25], as well as a hypothalamic regulatory dysfunction[1,8]. Finally, familial idiopathic hyperprolactinemia is a very rare condition which could result from abnormalities of the PRL gene, with the secretion of biologically inactive forms of PRL, or from PRL insensitivity due to a mutation of the PRL receptor gene[26].

The real prevalences of idiopathic hyperprolactinemia and macroprolactinemia are not fully established yet. In a Brazilian cohort of 115 hyperprolactinemic patients, 8 (7%) were classified as having Idiopathic hyperprolactinemia[17]. In two large European studies, 10%[27] and 29%[28] of patients with hyperprolactinemia were found to have idiopathic hyperprolactinemia. Macroprolactinemia prevalence has ranged from 18.5% when samples from reference laboratories were assayed[1,29,30]. A lower prevalence (10% to 26.1%) was encountered in patients from four endocrinology departments[11-17]. In a prospective study, we diagnosed macroprolactinemia in 19 of 115 (16.5%) consecutive patients with hyperprolactinemia[17].

Although most patients with macroprolactinemia display PRL levels <100 ng/mL[1,10-16], they are quite variable and may be as high as 404 ng/mL or more[1,10,13-15]. In the current study, as well as in previous ones[10,12,16], mean baseline PRL levels were similar in patients with idiopathic hyperprolactinemia or macroprolactinemia. Therefore, these patients cannot be reliably distinguished based only on clinical criteria and/or the magnitude of PRL levels elevation. This makes mandatory routine screening for macroprolactin in subjects with apparent idiopathic hyperprolactinemia.

Dopamine agonists, particularly cabergoline, are the treatment of choice for idiopathic hyperprolactinemia and prolactinomas[2,3]. In contrast, macroprolactinemia does not need to be treated[2,11,15]. In the current study, 22 macroprolactinemic patients (26.8%) were misdiagnosed, 15 of whom (68.2%) were misleadingly submitted to longterm cabergoline therapy. As also shown in other studies[11], the rate of PRL normalization was lower in patients with macroprolactinemia compared to those with monomeric hyperprolactinemia (40.0 vs 81.4%, $p = 0.02$).

In conclusion, our findings demonstrated that macroprolactinemia is often found in patients with an apparent idiopathic hyperprolactinemia. Thus, they highlight the importance of routine screening for macroprolactin in all patients with idiopathic hyperprolactinemia, regardless their clinical features, in order to avoid misdiagnosis and unnecessary treatment with dopamine agonists.

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