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:** The prevalence of macroprolactinemia, never systematically evaluated, was assessed during 20 months in consecutive symptomatic female patients with apparent idiopathic hyperprolactinemia routine and followed in two neuroendocrinology reference centers.. **Results**: A total of 82 patients (mean age: 36.1 ± 7.3 years, ranging from 25 to 50) were included, 69 (84.1%) were treated with cabergoline. The screening for macroprolactin was positive in 22 patients (26.8%), and 15 (68.2%) received incorrect long-term treatment with cabergoline. The clinical and demographic characteristics and baseline prolactin levels were compared in patients with true idiopathic hyperprolactinemia and in those with macroprolactinemia. **Conclusion:** Macroprolactinemia was observed in approximately 25% of patients with apparent idiopathic hyperprolactinemia. The findings highlight the importance of routine screening for macroprolactin in patients with idiopathic hyperprolactinemia, regardless of their clinical characteristics, 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 presents with increased serum prolactin (PRL) levels in the absence of known pituitary or central nervous system disease and other recognized causes[1,3,4].

The molecular size of circulating PRL is heterogeneous. The predominant form in healthy individuals and patients with prolactinomas is the monomeric PRL (molecular weight of 23 kDa). In contrast, the dimeric (4560 kDa) and macroprolactin (150170 kDa) forms correspond to less than 20% of the total PRL[5,6]. Macroprolactinemia occurs when the hyperprolactinemia serum contains mostly macroprolactin[1,7], which is formed by a complex of an IgG and a monomeric PRL in approximately 90% of cases[1,8]. Macroprolactin causes hyperprolactinemia due to low renal PRL clearance and decreased stimulation of the dopaminergic tonus[8]. In addition, macroprolactin has a high molecular mass and low biological activity and bioavailability[8,9], which explains why patients with macroprolactinemia often lack typical symptoms associated with hyperprolactinemia[8,11]. Therefore, macroprolactinemia 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.] However, the presence of galactorrhea, menstrual disorders, or erectile dysfunction does not exclude the diagnosis, as shown in 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 other causes of monomeric hyperprolactinemia[1,10,15-17].

This study aimed to determine the prevalence of macroprolactinemia during 20 months among symptomatic female patients with apparent idiopathic hyperprolactinemia, which was never systematically evaluated. Misdiagnosis in these cases could lead to unnecessary treatment with dopamine agonists.

METHODS

The study was performed in two neuroendocrinology centers at Recife, Pernambuco, Brazil (Endocrine Research Center of Pernambuco and Division of Endocrinology of *Hospital das Clínicas*, Federal University of Pernambuco). The clinical, laboratory, and demographic data were compared in patients with and without macroprolactinemia.

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

Results were expressed as percentages and mean values ± standard deviation (SD), unless otherwise stated. Categorical variables were compared using the chi-squared or Fisher's exact test when appropriate. A paired Student's t-test was performed for the comparative analysis of two means, and a p-value <0,05 was considered statistically significant.

The study was approved by local ethics and scientific committees, and all patients signed the informed consent form.

RESULTS

A total of 82 patients (mean age: 36.1 ± 7.3 years; ranging from 25 to 50) were included in the study; 69 (84.1%) were treated with cabergoline.

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

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

Table 1. Comparison of clinical, demographic, and laboratory characteristics at diagnosis in symptomatic female patients with macroprolactinemia and idiopathic hyperprolactinemia.

Characteristics	Macroprolactinemia (n = 22)	Idiopathic hyperprolactinemia (n = 60)	p -value
Age (years)	37.30 ± 9.65	35.70 ± 6.51	0.11
Mean PRL levels (ng/mL)	137.05 ± 72.12 (70 to 295)	156.45 ± 65.07 (75 to 286)	0.15
Isolated galactorrhea (%)	22.70 (n=5)	10.00 (n=6)	0.13
Isolated menstrual disorders (%)	68.20 (n=15)	56.70 (n=34)	0.24
Menstrual disorders and galactorrhea (%)	9.10 (n=2)	33.30 (n=20)	0.02
PRL normalization during CAB treatment (%)	40.00(n=6/15)	81.40 (n=44/55)	<0.01

CAB: cabergoline; PRL: prolactin

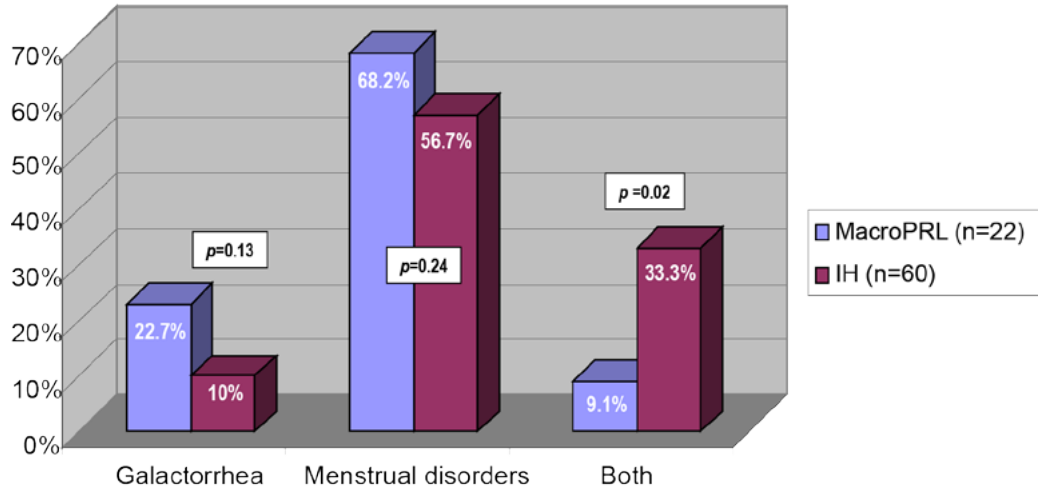

Figure 1. Presenting clinical characteristics of female patients with macroprolactinemia (MacroPRL) and idiopathic hyperprolactinemia (IH). The combination of galactorrhea and menstrual disorders was significantly lower in the macroPRL group than among IH patients (9.1% vs 33.3%, p = 0.02).

PRL levels did not significantly differ in patients with macroprolactinemia (70 to 295 ng/mL; mean of 137.05 ± 72.12) and in those with true idiopathic hyperprolactinemia (75 to 286 ng/mL; mean of 156.45 ± 65.07; p = 0.15). However, PRL levels lower than 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).

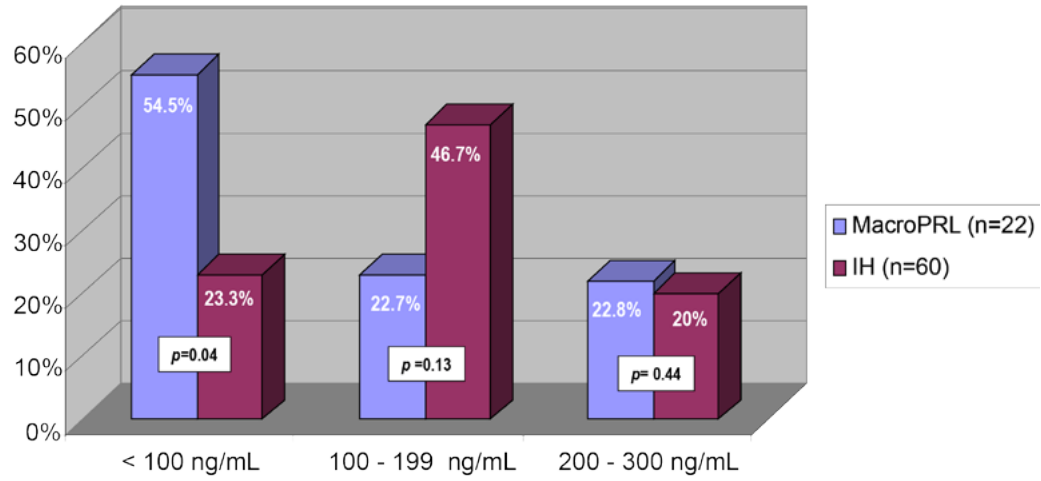

Figure 2. Distribution of patients with macroprolactinemia (MacroPRL) or idiopathic hyperprolactinemia (IH) according to their baseline prolactin (PRL) levels. Mean PRL levels were similar in both groups (p = 0,15).

DISCUSSION

This prospective study demonstrated positive macroprolactin in 26.8% of 82 symptomatic female patients with a previous diagnosis of idiopathic hyperprolactinemia. Other studies observed a prevalence of macroprolactinemia in individuals with idiopathic hyperprolactinemia ranging from 34.2% to 68.3%; however, the clinical profile was not mentioned[16,19].

Macroprolactinemia has been recognized in asymptomatic patients and volunteers in studies[1,5,6]. Macroprolactin was shown to exhibit low bioactivity and bioavailability[8,9], which may explain the lack of symptoms associated with hyperprolactinemia in most patients[10-15]. Accordingly, the 2011 Endocrine Society guidelines suggest screening for macroprolactin only in the investigation of asymptomatic hyperprolactinemic patients[2]. However, recent studies demonstrated galactorrhea and hypogonadism symptoms (oligo- and amenorrhea, infertility, and erectile dysfunction) often observed in patients with macroprolactinemia[10-15,19,20].

Macroprolactinemia was asymptomatic in 36 (56.3%) of 64 patients; the others presented hypogonadism symptoms and galactorrhea[20]. Conversely, only 11.5% with monomeric hyperprolactinemia were asymptomatic ($p < 0.001$). 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%, $p = 0.722$) did not show a significant difference between groups. However, 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]. Menstrual disorders or galactorrhea were equally prevalent in patients with or without macroprolactinemia, whereas the combination of these characteristics predominated in the idiopathic hyperprolactinemia group.

The results of this study corroborate literature[11-16,19] since among macroprolactinemia women, menstrual disturbances were observed in 12.4%, infertility in 4.9%, and galactorrhea in 1.8%[11-16,19]. Moreover, 50.7% of men with macroprolactinemia complained of erectile dysfunction[13,14].

Symptoms that motivate measurement of PRL are nonspecific and may occur coincidentally in patients who present hyperprolactinemia due to macroprolactin and associated conditions, such as idiopathic galactorrhea[21], chronic anovulation (e.g., polycystic ovary syndrome)[22], psychogenic erectile dysfunction[23], or non-functioning pituitary tumors[1,24]. Furthermore, macroprolactinemia patients may present prolactinomas or other causes of monomeric hyperprolactinemia[1,16,19], with PRL levels above the normal range after PEG precipitation[1,8].

Idiopathic hyperprolactinemia probably occurs from small prolactinomas that escape detection using magnetic resonance imaging[1-4]. Additionally, an autoimmune mechanism[25] and hypothalamic regulatory dysfunction[1,8] could be involved in some cases. Last, familial idiopathic hyperprolactinemia is a very rare condition that may result from abnormalities of the PRL gene, the secretion of biologically inactive forms of PRL, or PRL insensitivity due to a mutation of the PRL receptor gene[26].

The prevalence of idiopathic hyperprolactinemia and macroprolactinemia is not established in

the literature. In a Brazilian cohort of 115 hyperprolactinemic patients, 8 (7%) were classified with idiopathic hyperprolactinemia[17]. In two large European studies, 10%[27] and 29%[28] of patients with hyperprolactinemia had idiopathic hyperprolactinemia. Macroprolactinemia prevalence ranged around 18.5% when samples from reference laboratories were assayed[1,29,30]. A lower prevalence (10% to 26.1%) was observed in patients from four endocrinology departments[11-17]. Moreover, a prospective study diagnosed macroprolactinemia in 19 of 115 (16.5 %) consecutive patients with hyperprolactinemia[17].

Although most patients with macroprolactinemia presented PRL levels under 100 ng/mL[1,10-16], results vary and may reach 404 ng/mL or more[1,10,13-15]. In the present and previous studies[10,12,16], mean baseline PRL levels were similar in patients with idiopathic hyperprolactinemia or macroprolactinemia. Therefore, patients may not be distinguished based on clinical criteria and increased PRL levels, indicating a need for a mandatory routine screening for macroprolactin in patients with apparent idiopathic hyperprolactinemia.

Dopamine agonists, particularly cabergoline, are the choice treatment for idiopathic hyperprolactinemia and prolactinomas[2,3], although macroprolactinemia does not need to be treated2,11,15. In the present study, 22 macroprolactinemia patients (26.8%) were misdiagnosed, and 15 (68.2%) submitted to long-term cabergoline therapy. The rate of PRL normalization was lower in patients with macroprolactinemia compared with those with monomeric hyperprolactinemia (40.0 vs 81.4%, $p = 0.02$), corroborating other studies[11].

In conclusion, our findings demonstrated that macroprolactinemia is often observed in patients with an apparent idiopathic hyperprolactinemia. Thus, this study highlights the importance of routine screening for macroprolactin in all patients with idiopathic hyperprolactinemia to avoid misdiagnosis and unnecessary treatment with dopamine agonists, regardless of their clinical characteristics.

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