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Macroprolactinemia as a cause of hyperprolactinemia. Series of cases

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ABSTRACT

Macroprolactinemia is defined as the presence of prolactin with a molecular weight greater than 150 kDa. It can be confused with idiopathic hyperprolactinemia or with a prolactinoma. It is considered a benign variant and does not require medical treatment or follow-up. The objective of this article is to describe a series of patients with macroprolactinemia as a cause of hyperprolactinemia. Among fourteen cases, macroprolactinemia was found in eight (57.1%) and the majority (87.5%) presented with symptoms. Macroprolactinemia was frequent in this series of cases. The assessment of macroprolactinemia is useful in cases with apparently idiopathic hyperprolactinemia. (REV MEX ENDOCRINOL METAB NUTR. 2017;4:84-8)

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Key words: Macroprolactinemia. Hyperprolactinemia. Prolactinoma.

RESUMEN

La macroprolactinemia se define como la presencia de prolactina con un peso molecular mayor a 150 kDa. Puede confundirse con hiperprolactinemia idiopática o con un prolactinoma. Se considera una condición benigna y no requiere tratamiento médico o seguimiento. El objetivo de este artículo es describir una serie de pacientes con macroprolactinemia como causa de hiperprolactinemia. De 14 casos, se encontró macroprolactinemia en 8 (57.1%), y la mayoría (87.5%) se presentaron con síntomas. La macroprolactinemia fue frecuente en esta serie de casos. La evaluación de macroprolactinemia es útil en casos que aparentemente tienen hiperprolactinemia idiopática.

Palabras clave: Macroprolactinemia. Hiperprolactinemia. Prolactinoma.

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INTRODUCTION

Macroprolactinemia is a benign variant in which there is predominance of prolactin (PRL) with a molecular weight greater than 150 kDa that composed of PRL bound to IgG. Given its large size and limited availability for union to receptors, macroprolactin (macroPRL) is considered a variant with little biological activity. However, some individuals with macroprolactinemia can present with signs or symptoms of hyperprolactinemia. A possible explanation is the dissociation of the IgG-PRL complex with intermittent release of biologically active monomeric PRL[1].

Hyperprolactinemia is defined as idiopathic when there is failure to find a clear etiology. Remarkably, between 16 to 50% of patients with apparent idiopathic hyperprolactinemia are re-classified as having macroprolactinemia[2].

The response to dopamine agonists does not distinguish clearly between macroprolactinemia and real hyperprolactinemia. The administration of these drugs in patients with macroprolactinemia does not decrease serum PRL concentrations as much as in patients with prolactinoma, which suggests that the clearance or filtration of PRL in these individuals is delayed[3].

The Endocrine Society guidelines indicate that measurement of macroPRL should be considered in asymptomatic individuals with elevated PRL levels[4]. MacroPRL can be detected by the precipitation with polyethylene glycol (PEG) and by gel filtration chromatography (GFC); the latter is the gold standard for the diagnosis. However, this method is rarely used because of its high cost and low availability.

Although the PEG method is not quantitative, it correlates well with GFC and it is inexpensive and reproducible. This method has been widely used to assess the presence of macroPRL in serum from individuals with hyperprolactinemia[5-7].

When using the PEG method, false positive results may occur in individuals with an elevated globulin concentration. This is due to co-precipitation of PRL, with serum globulins increasing the amount of the monoPRL[8].

The objective of this study is to present a series of cases of individuals with macroprolactinemia at the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran. The hypothesis is that in patients with hyperprolactinemia, after ruling out physiological and pharmacological causes, macroprolactinemia frequency is high.

MATERIAL AND METHODS

We consecutively included patients with diagnosis of hyperprolactinemia (CIE E22.1). Inclusion criteria were the following: (i) men and women at least 18 years old with diagnosis of hyperprolactinemia, who were not receiving treatment with any dopamine agonist drug in the three months prior to the sampling, and (ii) men and women with a diagnosis of hyperprolactinemia with an adenoma who were receiving treatment with dopamine agonists in appropriate doses for at least two years without a satisfactory clinical, biochemical, and/or radiological outcome. These patients didn't stop the treatment during assessment. Exclusion criteria were: (i) patients with clear evidence of prolactinoma (PRL levels > 100 ng/ml with a hypophyseal tumor) and, (ii) patients in whom hyperprolactinemia was not confirmed.

Informed consent was obtained from all participants. In all cases, PRL was measured with an enzyme-amplified chemiluminescent immunoassay (Immulite® 1000 Siemens), calibrated (WHO 3° IS84/500), with sensitivity of 0.5 ng/ml (11 mIU/l).

Precipitation with PEG was performed at room temperature as follows: 300 µl of PEG (6000 Sigma) solution at a concentration of 250 g/l was added to 300 µl of serum. The mixture was homogenized and centrifuged for 30 minutes at 3,000 rpm. After that, PRL was measured on the supernatant. Intra- and inter-assay variation coefficients were 6.32 and 7.12%, respectively. Macroprolactinemia was defined when the estimated percentage of macroPRL was > 50% after precipitation with PEG.

In all patients with symptoms of hyperprolactinemia and elevated PRL concentration, a pituitary

magnetic resonance imaging (MRI) was requested as part of the usual clinical evaluation. In patients with progressive elevation of at least 50% in PRL concentrations, an MRI was also performed.

The following variables were obtained from the records: thyroid stimulating hormone (TSH) concentration, pregnancy test (if applicable), and creatinine concentration to rule out possible secondary causes. Serum globulins were also measured to rule out the possibility of a false positive result with the PEG method. Clinical characteristics were also recorded, including presence of headache, menstrual irregularities (oligomenorrhea defined by cycles with an interval of more than six weeks or amenorrhea defined as absence of menstruation for three or more months), galactorrhea, infertility (failure to achieve pregnancy after 12 months of intercourse without the use of contraceptives in women under 35 years old or after six months if older than 35), and campimetric visual defects. Microadenoma was defined as the presence of a tumor on the MRI < 10 mm and macroadenoma with a size ≥ to 10 mm.

Statistical analysis

Dimensional variables were evaluated for distribution and are described as mean and standard deviation (SD) or median and interquartile range, as appropriate. Frequencies and percentages are used to present categorical variables.

RESULTS

A total of 160 cases with diagnosis of hyperprolactinemia were evaluated in the period 2011 to 2014. After considering the inclusion and exclusion criteria and subsequent review of the clinical records, patients in whom there was no clear cause of hyperprolactinemia or in whom the usual treatment did not have the expected outcome (indicating the possibility of macroprolactinemia in the context of a non-functioning pituitary adenoma) were included.

The vast majority of patients with hyperprolactinemia were excluded due to physiological or pharmacological causes, or conclusive evidence of a prolactinoma.

We included 14 patients; 100% were women. The average age was 38 years. The median PRL concentration was 79.2 ng/ml and TSH average concentration was 2.17 mU/ml (only one person had a prior diagnosis of hypothyroidism, in treatment with levothyroxine at a satisfactory dose), mean creatinine and serum globulin concentrations were 0.68 mg/dl and 3.33 g/dl, respectively.

Most of the patients had amenorrhea or oligomenorrhea (64.3%). Galactorrhea was also a common manifestation, present in 71.4% at some point during the evaluation, being more frequently bilateral. Half of the patients referred headache.

Interestingly, half of the patients had evidence of a hypophyseal adenoma, and 85.7% of them were treated with a dopamine agonist, most commonly cabergoline (71.4%).

The characteristics of the studied population are described in table 1.

In eight (57.1%) of the 14 cases, macroprolactinemia was identified. In these cases, the median macroPRL percentage after precipitation was 62.9% (51.1-87.5). Of these eight cases only one (12.5%) had no symptoms. Table 2 shows the individual macroPRL percentage after precipitation in each case.

DISCUSSION

This series of cases shows that macroprolactinemia is frequent in individuals considered as having idiopathic hyperprolactinemia. Macroprolactinemia was present in 57.1% of the cases, and 50% of these subjects had a hypophyseal adenoma. In contrast to the reported data, the majority (87.5%) presented symptoms.

The prevalence of macroprolactinemia in the general population is low (0.2% in females and 0.02% in men)[9,10], although other studies have reported a

Table 1. Clinical and biochemical characteristics of the studied population (n = 14)

Variable	
Age (years)	38.4 ± 10.7
Age of menarche (years)	12.3 ± 1.3
PRL (ng/ml)	79.2 (53.1-150.0)
TSH (mU/ml)	2.17 ± 1.20
Creatinine (mg/dl)	0.68 ± 0.13
Globulin (g/dl)	3.30 ± 0.27
Presence of adenoma	7 (50.0)
Macroadenoma	4 (28.6)
Presence of arachnoidocele	5 (35.7)
Amenorrhea/oligomenorrhea	9 (64.3)
Galactorrhea	10 (71.4)
Previous pregnancy	4 (28.6)
Infertility	5 (35.7)
Headache	7 (50.0)
Campimetric defect	2 (14.2)
Dopaminergic agonist treatment	12 (85.7)

Data are presented as means and SD, median (interquartile range), or frequency and %.
PRL: prolactin; TSH: thyroid stimulating hormone.

Table 2. Macroprolactin percentage after precipitation with polyethylene glycol in the studied cases (n = 14)

Case number	MacroPRL after precipitation (%)
1	39.0
2	69.0
3	50.0
4	39.0
5	24.9
6	88.3
7	93.9
8	56.8
9	51.0
10	51.0
11	87.4
12	40.0
13	39.0
14	51.2

MacroPRL: macroprolactin.

higher prevalence[11]. However, in patients with hyperprolactinemia, macroprolactinemia prevalence varies from 15 to 26%[6,10,12]

In the cohort of Leslie, et al. (2001)[12] the presence of macroprolactinemia was demonstrated in 26% of 1,225 patients with a PRL concentration > 700 mIU/l (33 ng/ml). In 55 patients identified as having macroprolactinemia, clinical symptoms of hyperprolactinemia were rarely present. In 2010, Wallace, et al.[10] published the results of a cohort after a median follow-up of nine years. The results in 51 patients indicated a median age at presentation of 41 years (18-55); PRL concentration at diagnosis averaged 1,885 mIU/l (89 ng/ml) and at follow-up 1,370 mIU/l (65 ng/ml). Twelve patients (24%) had headache, five patients (10%) oligomenorrhea, and two (4%) galactorrhea. There was no visual impairment and none developed autoimmune diseases. A microadenoma was identified in four patients without other hypophyseal hormone abnormalities. It was concluded that macroprolactinemia is a benign variant and that treatment with dopamine agonists and long term follow-up are not necessary.

Hattori in Japan, the Wallace and Associates Group, and other authors have suggested that macroprolactinemia should be ruled out in patients with hyperprolactinemia. A high percentage of patients with macroprolactinemia have abnormalities on imaging studies. MacroPRL detection could help to identify and distinguish patients with true hyperprolactinemia due to an adenoma, requiring treatment with dopamine agonists, or those with macroprolactinemia and pituitary lesions requiring only monitoring or surgical treatment[13,14] For this reason, macroprolactinemia identification should be included in the workup of hyperprolactinemia in order to avoid overtreatment in individuals with this benign entity and unnecessary costs of treatment and imaging studies.

Limitations of this study should be acknowledged. This is a small series and the results cannot be generalized. In order to determine the prevalence of macroprolactinemia, further studies measuring macroPRL in all cases with hyperprolactinemia are needed. In addition, the follow-up of individuals with this entity is needed to confirm its benign nature.

In conclusion, macroprolactinemia was a frequent finding in this series of subjects with hyperprolactinemia. Given the frequency of this entity and

being apparently a benign variant, it is useful to include its detection in the assessment of patients with apparently idiopathic hyperprolactinemia.

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