

Case Report

Macroprolactinemia. Is treatment necessary?

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ABSTRACT

A 26-year old symptom-free woman was admitted to our Clinic for evaluation of hyperprolactinemia. The patient, who had normal menstrual cycles, was found accidentally to have a cystic adnexal mass and was placed on oral contraceptives (OC) for 3 months. During the first OC-cycle a bilateral breast nipple discharge was noticed and an elevated serum prolactin (PRL) was detected (2.7 nmol/l). The OC was discontinued and bromocriptine therapy was started. Serum PRL levels were restored and spontaneous menses resumed. The Pituitary magnetic resonance imaging (MRI), the anterior pituitary function, assessed by dynamic tests, and the thyroid hormone levels were normal. Upon bromocriptine discontinuation, PRL levels increased to 13.8 nmol/l. Poly-ethylene-glycol precipitation of the patient's serum, in two consecutive measurements, demonstrated the presence of macroprolactinemia. Since the patient was asymptomatic, a dopamine agonist was not resumed. Macroprolactinemia is characterized by most authors, as a benign condition with no clinical implications. However, a number of investigators challenge this view, suggesting that in some cases mild symptomatology is present possibly requiring therapeutic intervention.

Key words: hyperprolactinemia, macroprolactinemia

INTRODUCTION

In the majority of patients with hyperprolactinemia monomeric prolactin (PRL) namely PRL with a molecular weight of 23K DA predominates. Nevertheless, in some patients with hyperprolactinemia high molecular weight forms of PRL are primarily detected. These forms of PRL are the big PRL (molecular

weight 50-60 K DA) and the big-big PRL (macroprolactin) with a molecular weight greater than 100 K DA.

Macroprolactinemia is a term applied to cases with high prolactin concentrations in which big-big prolactin predominates. In such cases the recognition of high molecular weight PRL can be achieved by gel filtration chromatography or by a simplified method using polyethylene glycol precipitation (PEG). If macroprolactin is present in serum it is precipitated by glycol while the monomeric remains in the supernatant. The introduction of the latter method has greatly facilitated the diagnosis of macroprolactinemia which is suspected when high prolactin values are detected in as-

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ymptomatic patients.

In the present report we describe a woman with hyperprolactinemia, accidentally detected and in whom macroprolactinemia was finally diagnosed.

CASE REPORT

A 26-year old white woman was admitted to our Clinic for evaluation of hyperprolactinemia detected 6 months previously. The patient had spontaneous menarche at age 11 and normal menstrual periods since then. Her cycles were of 28 days duration and menstrual bleeding lasted 4-5 days. The patient had undergone total thyroidectomy for multinodular goiter and had been on L-thyroxine substitution therapy (150mg per day). During a period of psychological distress she noticed midcycle bleeding, lasting 2-5 days, for two consecutive months. Because of this she was subjected to pelvic ultrasonography which revealed a 5.5 x 4cm cystic right adnexal mass. The patient was subsequently placed on therapy with oral contraceptives (OC) for three months. During that period the patient noticed bilateral breast nipple discharge. Serum prolactin (PRL) measured for the first time was found 2.7nmol/l. Oral contraceptives were discontinued and bromocriptine therapy (5mg/day) was advised by her private gynecologist without further work-up. Under this treatment, serum PRL levels returned to normal (0.29nmol/l) and the menstrual cycles were regular following oral contraceptive withdrawal. After 4 months of bromocriptine therapy, an attempt was made to discontinue bromocriptine treatment. Two weeks after stopping bromocriptine, serum PRL levels increased to 13.8nmol/l.

The patient was admitted to our endocrine ward for complete work-up of her hyperprolactinemia. During her hospitalization the serum PRL levels ranged from 4.5-8.4nmol/l. Pituitary gland MRI was normal. The thyroid hormone levels were within normal limits: (TSH 0.1mIU/l, FT₃ 0.43pmol/l, FT₄ 19.3pmol/l. Anterior pituitary function, assessed by IV insulin tolerance test, was normal. Pregnancy was excluded by a low β -HCG level (1mIU/l).

The serum PRL levels were subsequently measured after precipitation of the patient's serum with polyethylene-glycol. With this method, serum PRL levels were normal on two consecutive measurements (0.61 and 0.65nmol/l). The patient was discharged from our

hospital with the diagnosis of macroprolactinemia and without any medication. Following her discharge she has been symptom-free and reports regular menstrual cycles lasting 28 days.

DISCUSSION

Macroprolactinemia has been repeatedly documented as a cause of elevated PRL levels over the past two decades¹. Prolactin circulates in human serum in three forms: 1) monomeric PRL (molecular weight 23 Kdalton), which is the usual form and has the highest biologic activity, 2) big PRL (molecular weight 50-60 Kdalton) and 3) big – big PRL or macroprolactin (molecular weight 150-170 Kdalton). The last two forms seem to result from complexes of monomeric PRL with PRL-binding antibodies and have reduced biologic activity due to their difficulty in crossing the capillary wall²⁻⁵. The PRL-binding antibodies act as a buffer system for the monomeric PRL molecules and are responsible for pseudo-hyperprolactinemia.

The prevalence of macroprolactinemia ranges from 10-30% of hyperprolactinemic patients, depending on the method employed and the definition used⁶⁻⁸. The most validated method for the detection of macroprolactinemia is gel filtration chromatography which, however, is expensive and difficult to perform⁷. Recently, a simpler screening method using polyethylene glycol (PEG) has been employed for the detection of macroprolactinemia. Macroprolactin, if present in the serum, is precipitated by prior incubation with PEG. In general, recovery rates less than 40% are attributed to macroprolactinemia^{6,8-10}.

The clinical relevance of macroprolactinemia is a matter of debate. The majority of patients with macroprolactinemia lack the classical symptoms of PRL excess, such as menstrual irregularities, galactorrhea or subfertility, and have normal pituitary gland on MRI. Dopamine agonists, therefore, are not necessary and many clinicians feel that no pharmacological intervention and only careful follow-up is warranted¹¹⁻¹⁵. This view, however, has recently been questioned. Vallette-Kasic⁶ reported a series of 106 patients with macroprolactinemia followed up over a 10-year period. Although the majority of these patients were asymptomatic and had uneventful pregnancies, a number of patients reported symptoms associated with hy-

perprolactinemia such as menstrual irregularities or subfertility. The dilemma of therapeutic intervention is exaggerated by MRI findings suggestive of a pituitary adenoma. In such cases the question as to whether or not this is a coincidental, non-functioning adenoma or is related to the hyperprolactinemia is difficult to answer. Our patient was completely asymptomatic and ovulation was confirmed in two consecutive cycles by measuring serum progesterone levels on day 21 of the menstrual cycle. Therefore, we could not ascribe a clinical relevance to macroprolactinemia except for the occasional nipple discharge. The normalization of prolactin level in our patient by the initial administration of bromocriptine is not easily explained. It is possible that the hyperprolactinemia previously detected was a response to her reported stress which led to the antibody formation and subsequent macroprolactinemia detected during hospitalization in our clinic. As regards the therapeutic intervention, the final choice of treatment in cases of macroprolactinemia should be individualized. In the majority of cases the condition is benign and no treatment is required. In certain cases, however, especially when symptoms are present, a trial of dopamine agonist treatment may be warranted.

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