Response of Macroprolactinemia to Dopamine Agonists

Makroprolaktineminin Dopamin Agonistlerine Cevabı

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Abstract

Macroprolactinemia, defined as hyperprolactinemia with a predominance of the big big prolactin (macroprolactin) isoform, is considered idiopathic and poorly symptomatic. Although macroprolactinemia has been considered to be a cause of apparent resistance to antiprolactinemic drugs, prolactin (PRL) normalization with dopaminergic treatment cannot exclude macroprolactinemia.

We report three cases with macroprolactinemia, whose PRL and macroprolactin levels were decreased and hyperprolactinemic symptoms were improved with dopamine agonists. *Turk Jem 2008; 12: 83-5*

Key words: Macroprolactinemia, dopamine agonists, hyperprolactinemia

Özet

Makroprolaktineminin ileri tetkik ve tedavi gerektirmeyen selim bir durum olduğu öne sürülmesine rağmen, bazı çalışmalarda makroprolaktinemide hiperprolaktinemik sendromun klinik ve radyolojik özelliklerinin görülebileceği iddia edilmektedir. Bu görüşü destekleyen çalışmalarda, dopamin agonistiyle tedavi edilen makroprolaktinemili hastalarda total prolaktin (t-PRL) ve makroprolaktin düzeyinde düşme elde edilmiştir. Bununla birlikte, makroprolaktineminin, antiprolaktinemik ilaçlara rezistansın sebebi olduğunu iddia eden çalışmalar da mevcuttur. Burada bromokriptinle tedavi edilen üç makroprolaktinemili olgu sunulacaktır. *Turk Jem 2008; 12: 83-5*

Anahtar kelimeler: Makroprolaktinemi, dopamin agonistleri

Introduction

Prolactin (PRL), a polypeptide hormone, circulates in three discrete forms. These include a monomer with a molecular mass of 23 kDa, which accounts for approximately 85% of PRL present in normal individuals, a 50 kDa species accounting for 10% to 15% of total PRL, and a small but variable amount of a high molecular mass form (150-170 kDa) termed "big big" prolactin or macroprolactin (1-5).

Most studies have suggested that macroprolactinemia is a benign condition that does not need treatment or further investigation (1,5,6). Other studies, however, suggest that macroprolactinemia is not a benign condition; some hyperprolactinemic symptoms (irregular menses, galactorrhea, infertility) and rarely pituitary adenomas are associated with macroprolactinemia (7).

Some studies suggest that macroprolactinemia is a cause of apparent resistance to antiprolactinemic drugs. Conversely, in some cases with macroprolactinemia, dopaminergic treatment decreased serum macroprolactin levels and improved hyperprolactinemic symptoms. In addition, it should be kept in mind that spontaneous improvement or resolution of hyperprolactinemic symptoms may occur in some patients with macroprolactinemia (8,9).

We present three macroprolactinemic patients whose hyperprolactinemic symptoms were improved after treatment with dopamine agonists.

Materials and Methods

Patients

We studied three patients with hyperprolactinemia. All samples with a PRL value >24.1 ng/mL were submitted to the polyethylene glycol (PEG) precipitation test.

None of the patients had been taking any pharmacological agents known to cause elevation in PRL levels; none had hypothyroidism, polycystic ovarian syndrome, renal failure, or liver cirrhosis; and none had symptoms of intercostal nerve stimulation or pituitary stalk injury.

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The male patient was questioned about infertility, and female patients were questioned about infertility and irregular menses and examined for galactorrhea. Menses were accepted as irregular when intervals between were longer than 40 days.

Polyethylene Glycol (PEG) Precipitation Test

Macroprolactin assessment was performed by PEG precipitation in serum samples with prolactin levels exceeding the normal reference interval. The method which has been previously described by Hattori et al (10) and extensively validated by Olukoga and Kane (8) was performed as follows: Precipitation with PEG was carried out by adding 200 µL of serum to 200 µL of 25 g/dL PEG 6000 solution. The PEG solution was freshly prepared. After thorough mixing and centrifugation at 3000 rpm for 30 min, the supernatant was removed for analysis, and PRL assay was performed immediately. Prolactin in the supernatant was considered to be free of macroprolactin, because PEG precipitates substances with molecular weight more than 100 kDa.

Prolactin recovery (%) was derived for each serum sample as a percentage of the PRL measured in the supernatant relative to that measured in the untreated serum [(PRL in the supernatant x2 / PRL in the serum) x100]. In this study, a recovery of <40% was taken as an indicator of the presence of significant amounts of macroprolactin (8,10).

Case Reports

Patient 1: A 31-year-old woman applied to our outpatient clinic, complaining of irregular menses. She did not have galactorrhea or infertility (she had a one-year old child). Her axillary and pubic hair were normal; her height was 161 cm and weight was 62 kg.

Anterior pituitary hormones were measured in the follicular phase of the patient's menstrual cycle. Serum PRL was 54.7 ng/mL (reference interval for females:3.4-24.1 ng/mL), macroprolactin was 34.3 ng/mL, follicle-stimulating hormone (FSH) was 9.1 mIU/mL (reference interval in follicular phase for females: 3.5-12.5 mIU/mL), luteinizing hormone (LH) was 10.3 mIU/mL (reference interval in follicular phase for females: 2.4-12.6 mIU/mL), estradiol level was 43.5 pg/mL (reference interval in follicular phase for females: 24.5-195 pg/mL). Other anterior pituitary hormone levels and magnetic resonance imaging (MRI) of the pituitary were normal. Fasting glucose was 92 mg/dL and fasting insulin was 3.4 IU/mL. Her transvaginal ultrasound was normal (no sign of polycystic ovary). The patient was treated with bromocriptine, 2.5 mg twice daily for 3 months. Her menses became regular, serum PRL decreased to 3.8 ng/mL, and macroprolactin was 2.8 ng/mL 3 months after starting treatment.

Patient 2: A 36-year-old man was referred to our outpatient clinic because of impotence and decreased libido. He did not have gynecomastia or galactorrhea. His testicles were of normal size and consistency, pubic and axillary hair were normal. Serum PRL was 63.7 ng/mL (reference interval for males: 4.1-18.4 ng/mL), macroprolactin was 52.1 ng/mL, FSH was 12.8 mIU/mL (reference interval for males: 1.5-12.4 mIU/mL), LH was 7.4 mIU/mL (reference interval for males: 1.7-8.6 mIU/mL), and testosterone was 3.54 ng/mL (reference interval for males: 2.8-8 ng/mL). Other anterior pituitary hormone levels and MRI of the pituitary were normal. He was treated with bromocriptine, 2.5 mg twice daily for 3 months. Three months after starting treatment, the patient's libido and impotence improved; his PRL was 20.7 ng/mL, macroprolactin was 16.7 ng/mL, FSH was 11.2 mIU/mL, LH was 6.8 mIU/mL, and testosterone was 4.95 ng/mL.

Patient 3: A 21-year-old woman was referred to our outpatient clinic because of galactorrhea. Her menses were regular and she did not have infertility (she had a one-year old child). Serum PRL was 115.6 ng/mL, macroprolactin was 95.6 ng/mL, FSH was 8.7 mIU/mL, LH was 5.6 mIU/mL, and estradiol level was 39.8 pg/mL. Other anterior pituitary hormone levels and MRI of the pituitary were normal. She was treated with bromocriptine, 2.5 mg twice daily for 3 months. After 3 months of treatment, galactorrhea disappeared, serum PRL was 41.7 ng/mL, and macroprolactin was 36.3 ng/mL.

Discussion

Macroprolactinemia may be observed in both sexes (11-16), but women represent 89% of the published cases (11,17,18). Most studies have suggested that macroprolactinemic patients do not need any treatment, since many patients who were reported to have macroprolactinemia do not present with the typical clinical manifestations of hyperprolactinemic syndrome (13,19,20). But in more recent series, including that of Vallette-Kasic, a significant proportion of patients with macroprolactinemia appeared to suffer from the symptoms commonly associated with hyperprolactinemia. Valette-Kasic determined menstrual disorders (39%), infertility (29%) and galactorrhea (42%) in 106 macroprolactinemic patients (21).

Monomeric PRL has been shown to preferentially decrease (21,22) and the normalization of PRL levels was observed in many cases on dopamine agonist therapy (22). Macroprolactinemia has been considered to be a cause of resistance to antiprolactinemic drugs, but the normalization of PRL by dopaminergic treatment cannot exclude macroprolactinemia. Some studies have shown that after pituitary stimulation or suppression with dopamine antagonists or agonists, the increase or decrease in serum monomeric prolactin (m-PRL), were followed by similar changes in macroprolactin concentration. Although the results of some studies indicate that spontaneous improvement or resolution of symptoms may occur in some patients with macroprolactinemia, Olukoga and Kane determined in patients with macroprolactinemia that dopamine agonists decreased macroprolactin levels and improved hyperprolactinemic symptoms, and cessation of the therapy with dopamine agonists resulted in rebound hyperprolactinemia in all patients (8). This response suggests the presence of a persistent stimulus to prolactin secretion in macroprolactinemia. This stimulus is likely to be the mapping of free prolactin by the immunoglobulin binder. It was notable in the study of Olukoga and Kane that m-PRL levels of patients whose hyperprolactinemic symptoms disappeared with dopamine agonists were normal before the treatment, but their macroprolactin levels were high (8). Strachan suggested that macroprolactin might have biological activity, and a trial of dopamine agonist therapy may be offered if a patients has hyperprolactinemic symptoms (3). However, if dopamine agonist treatment is considered for patients with macroprolactinemia, the need for ongoing treatment should be reviewed regularly, and the therapy should be withdrawn if there is no symptomatic improvement (3).

The first and the third patients had normal serum m-PRL but high levels of macroprolactin. Thus, hyperprolactinemic symptoms of these patients were thought to be due to macroprolactin. Treatment with dopamine agonists improved hyperprolactinemic symptoms and decreased both m-PRL and macroprolactin levels. Since the second patient had high serum m-PRL and high macroprolactin levels, hyperprolactinemic symptoms might be due to m-PRL in this patient, but dopamine agonist treatment decreased both m-PRL and macroprolactin levels.

In conclusion, although many studies have concluded that macroprolactinemic patients do not need treatment, treatment of macroprolactinemic patients with dopamine agonists can sometimes decrease both m-PRL and macroprolactin levels and improve hyperprolactinemic symptoms.

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