

Macroprolactinemia in Patients Presenting with Hyperandrogenic Symptoms and Hyperprolactinemia

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Macroprolactinemia may account for a significant number of hyperprolactinemic sera including hyperandrogenic women and this may lead to unnecessary diagnostic and therapeutic procedures and false exclusion of PCOS. The aim of this study was to evaluate macroprolactinemia in women with hyperandrogenic symptoms and hyperprolactinemia.

Materials and Methods: In a series of 200 hyperandrogenic women aged 14-40 year, presenting to the endocrine clinic of Ghaem Hospital between 2004-2006, serum prolactin was measured. Those with hyperprolactinemia (prolactin >35 µg/L), were studied for the presence of macroprolactinemia using the polyethyleneglycol precipitation test (PEG).

Results: Mean age of hyperandrogenic women was 24.0±5.6 years; 38 (19%) of the patients had serum prolactin >30 µg/L and in 9 of them the rise was >35 µg/L. Macroprolactinemia was detected in 5 of those with serum prolactin >35 µg/L who also carried the diagnosis of PCOS. In the remaining 4 patients there was true hyperprolactinemia and prolactin remained elevated after PEG precipitation test (52±10, vs 48±9 µg/L, respectively).

Conclusion: It is necessary to rule out macroprolactinemia in women presenting with hyperandrogenic symptoms and hyperprolactinemia to prevent false exclusion of PCOS. This may help to avoid expensive and unnecessary diagnostic procedures and inappropriate use of dopaminergic agonists.

Key Words: Macroprolactinemia, Hyperprolactinemia, Hyperandrogenism, polyethyleneglycol precipitation test

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Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy in women during their reproductive years. Oligomenorrhea and clinical or biochemical hyperandrogenism are two main diagnostic criteria, but for confirmation of diagnosis other causes such as hyperprolactinemia should be ruled out.¹⁻⁴ Hyperprolactinemia is common in women presenting with hyperandrogenic symptoms and menstrual disturbances,⁴⁻⁶ and the diagnosis of PCOS cannot be substantiated in these women.

Prolactin exists in three different molecular sizes in human serum: small or monomeric (90% of serum prolactin), big and big big (macroprolactin).⁷⁻⁹ In most studies^{10,11} macroprolactin is defined as a complex of monomeric prolactin and immunoglobulin G, but in some of them it is referred to as a complex of prolactin and glucose or aggregation of prolactin molecules.¹⁰⁻¹³ Macroprolactin has lesser clearance¹²⁻¹⁶ and bioactivity^{8,10,17,18} than monomeric prolactin and may

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constitute the dominant form (more than 80%) of serum prolactin in some people.⁷

Association of macroprolactinemia in hyperandrogenic women can result in unnecessary and expensive diagnostic procedures and inappropriate treatment. The standard test for diagnosis of macroprolactinemia is Gel Filtration Chromatography. However the procedure is expensive and time consuming,¹⁹ whereas acceptable results can be achieved by Polyethyleneglycol (PEG) precipitation that is a rapid and non expensive test.^{20,21} The aim of this study was to answer to this question if macroprolactinemia or true monomeric hyperprolactinemia may be the cause of hyperprolactinemia in women with hyperandrogenic symptoms and hyperprolactinemia.

Materials and Methods

We evaluated 200 hyperandrogenemic women aged 14-40 years, presenting to the endocrine clinic of Ghaem Hospital from September 2004 to September 2006. Hyperandrogenism was defined as acne and hirsutism (Ferriman-Gallway score >7) or androgenic hair loss. After taking history and physical examination, serum prolactin was measured in all patients using the immunoradiometric assay. Hyperprolactinemia was diagnosed if serum prolactin level was more than normal (>30 µg/L). It has been shown in previous studies that in serum prolactin <35 µg/L (700 mu/L), macroprolactin does not constitute a significant proportion of serum prolactin.²² Therefore, when serum prolactin was >35 µg/L, serum prolactin was measured again in fasting state, by immunoradiometric assay (IRMA), with Kavoshyar kit using Gamma Counter (Gammatic 1, Swiss). In addition, 200 µL of patient serum was incubated with similar volume of PEG for 10 minutes at room temperature in pH=7.4 and centrifuged at 1800 G for 15 minutes. After pre-

cipitation, prolactin was measured again in patient serum treated with PEG by IRMA method and the difference was determined and expressed as recovery rate. Macroprolactinemia was diagnosed if the serum prolactin after PEG was equal or less than 40% of initial serum prolactin or in other words if precipitation after PEG was more than 60%.^{21,22}

Results

The patients were 200 women aged 24.0±5.6 years (range 14-40), serum prolactin was higher than 30 µg/L in 38 (19%) patients. In 9 women (4.5%), hyperprolactinemia was significant (>35 µg/L). In these patients evaluation for macroprolactin was performed with PEG precipitation test. Serum prolactin decreased more than 60% in 5 patients and macroprolactinemia was confirmed. Serum prolactin was within normal limits in these women after PEG precipitation (Table 1).

Mean serum prolactin in these women was 89±61 and decreased to 17.6±6.2 µg/L after precipitation with PEG (80% precipitation on average). Mean body mass index (BMI) in these patients was 28.6±2.9 kg/m². All of these patients have diagnostic criteria for PCOS.

In 4 patients there was true hyperprolactinemia. Mean serum prolactin in these patients was 52±10 and decreased to 48±9 µg/L after PEG precipitation; therefore, less than 7% precipitation occurred after PEG. Mean BMI in these patients was 31.7±8.3 kg/m². Hypophyseal microadenoma was seen in one patient in imaging studies and she was diagnosed as microprolactinoma. Three other patients had normal imaging of hypophysis and were diagnosed as idiopathic hyperprolactinemia. Clinical and paraclinical findings of patients are summarized in Table 1.

Table 1. Clinical and paraclinical findings of patients with hyperandrogenism and hyperprolactinemia

No.	Age (years)	BMI (Kg/m ²)	Acne	Hair loss	Menstruation disturbances	Hirsutism	Prolactin (µg/L)	Prolactin after PEG (µg/L)	Diagnosis of macroprolactinemia
1	20	28	-	+	+	-	35	10	+
2	19	23	+	-	+	+	190	12	+
3	27	26	-	-	+	+	56	24	+
4	22	26	+	-	+	+	64	20	+
5	22	31	+	+	+	+	100	22	+
6	24	32	+	+	+	-	56	50	-
7	37	37	-	-	+	+	40	38	-
8	19	28	+	-	+	+	64	60	-
9	25	30	-	+	+	+	48	46	-

Discussion

In spite of many studies having been performed about the cause of hyperprolactinemia in hyperandrogenic women, there is not enough information available on this association. Increased serum estron⁴ and change in dopaminergic and opioid tone of hypothalamus may be the cause of this association. Evaluation of the patients presented with hyperandrogenism and hyperpprolactinemia is difficult because there is no accepted protocol for this diagnosis.²³ Hyperprolactinemia caused by macroprolactinoma, may impose expensive, unnecessary diagnostic procedures and inappropriate treatment and it may delay the diagnosis and treatment of the main background disease.

Recently the PEG precipitation test has been used for determination of macroprolactinemia with good results and reasonable prices. In this study, we used this test for determination of macroprolactinemia in women

with hyperandrogenic symptoms and significant hyperprolactinemia. Evaluation of 200 women with hyperandrogenism showed that 19% of patients had hyperprolactinemia, which was significant in 9 (4.5%). In 5 patients (55%), macroprolactinemia was confirmed with the PEG precipitation test. These patients had diagnostic criteria of PCOS; in 4 patients, there was true hyperprolactinemia. In a similar study performed in Spain,²⁴ hyperprolactinemia was present in 8 of 109 women with hyperandrogenic symptoms and 4 had macroprolactinemia.

In conclusion, macroprolactinemia may be the cause of hyperprolactinemia in women with hyperandrogenic symptoms. Screening for macroprolactin with the inexpensive and simple PEG precipitation with PEG is recommended for prevention of expensive and unnecessary diagnostic procedures and inappropriate treatment in such patients.

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