Macroprolactin as a Cause of Hyperprolactinemia: Clinical and Radiological Features

Hiperprolaktineminin Bir Sebebi Olarak Makroprolaktin: Klinik ve Radyolojik Özellikler

Assim Alfadda

Department of Internal Medicine, College of Medicine and King Khalid University Hospital, King Saud University, Saudi Arabia

Abstract

Objective: The aim of this study was to determine the prevalence of macroprolactin in patients with hyperprolactinemia in our region, and to determine the clinical and neuroradiological features of the affected individuals.

Materials and Methods: We used the Roche Elecsys Prolactin assay (Prolactin II) with polyethylene glycol precipitation to identify macroprolactin; recovery of ≤40% was considered to represent significant macroprolactinemia. Of 156 consecutive patients with hyperprolactinemia, macroprolactin was found in ten (6.4%). Clinical records of these patients were reviewed.

Results: Of ten patients with macroprolactinemia, two males presented with infertility and two with decreased libido and erectile dysfunction. Females presented with menstrual dysfunction, with or without infertility. Pituitary adenomas were identified in two of seven patients who underwent neuroimaging. Dopamine agonists were prescribed to seven patients; their symptoms were not affected by this therapy.

Conclusions: Macroprolactin is a cause of misdiagnosis and inappropriate treatment in patients with hyperprolactinemia. It is important to be aware of the extent to which the assay system used in the measurement of prolactin may detect macroprolactin, and to have a available validated method to confirm its presence. This will ensure appropriate management for patients with this benign condition. *Turk Jem 2008; 12: 46-9*

Key words: Macroprolactin, prolactin, pituitary adenoma, pituitary imaging

Özet

Amaç: Bu çalışmanın amacı, bölgemizde hiperprolaktinemisi olan hastalardaki makroprolaktin prevalansını ve makroprolaktinemisi mevcut kişilerin klinik ve nororadyolojik özelliklerini belirlemektir.

Gereç ve Yöntemler: Roche Elecsys" prolaktin ölçüm yöntemini (prolaktin II) kullanarak, polietilen glikol çöktürmesi ile makroprolaktin ölçüldü. Yöntem sonucunda prolaktin düzeylerinin ≤%40 toparlanmasi anlamli makroprolaktinemi olarak kabul edildi. Hiperprolaktinemisi mevcut 156 ardışık hastanın 10' unda (%6.4) makroprolaktin tespit edildi. Bu hastaların klinik kayıtları gözden geçirildi.

Bulgular: Makroprolaktinemisi mevcut 10 hastadan iki erkek, infertilite ile, iki erkek ise azalmış libido ve erektil disfonksiyon ile başvurdular. Altı kadın hastanın başvuru nedeni, infertilite ile birlikte veya infertilite olmadan adet düzensizliği idi. Görüntüleme gerçekleştirilen 7 hastanın ikisinde hipofiz adenomu tespit edildi. Yedi hastaya dopamin agonisti verildi. Fakat semptomlar bu tedaviden etkilenmedi.

Sonuç: Makroprolaktin, hiperprolaktinemili hastalarda yanlış tanının ve uygun olmayan tedavinin önemli bir nedenidir. Prolaktin ölçümünde kullanılan yöntemlerin makroprolaktini tespit edip etmediğinin bilinmesi ve makroprolaktinemiyi doğrulamak için geçerli bir yöntemin bulunması önemlidir. Bu durum, makroprolaktinemisi mevcut kişilere uygun yaklaşımın sağlanmasına ve gereksiz tedavi girişimlerinin engellenmesine yol açacaktır. *Turk Jem 2008; 12: 46-9*

Anahtar kelimeler: Makroprolaktin, prolaktin, hipofiz adenomu, hipofiz görüntülemesi

Introduction

It has been established that the sera of healthy individuals contain several forms of prolactin (PRL), including monomeric PRL of 23 kDa, which constitutes 85% to 90% of total PRL; big PRL of (45-60 kDa), which is a covalently bound dimer of PRL and constitutes 10% to 15%, and big-big PRL, or macroprolactin, (>100 kDa) which accounts for a small and variable percentage of circulating PRL (1,2). In most cases, macroprolactin represents a large antigen-antibody complex and is considered biologically inactive

Address for Correspondence: Assim Alfadda, MD, Department of Internal Medicine, College of Medicine, King Saud University, P.O. BOX: 2925, Riyadh 11461, Saudi Arabia. Tel.: +01 467-1497 Fax: +01 467-2575 E-mail: aalfadda@ksu.edu.sa **Recevied:** 31.03.2008 **Accepted:** 24.05.2008

(2-6). Several groups have reported variable detection of macroprolactin by PRL immunoassays (7,8). In some individuals, most of the circulating PRL may be in the macroprolactin form, causing pseudohyperprolactinemia. This may be a cause of misdiagnosis, unnecessary investigation, and incorrect treatment (9,10). The prevalence of macroprolactinemia in hyperprolactinemic population varies from 10% to 46%, depending on the population studied and the assay used for PRL measurement (11,12). The need to differentiate between true hyperprolactinemia, which needs treatment, and the apparently benign clinical condition of macroprolactinemia has been recommended by several authors (10). However, routine screening for the presence of macroprolactin has not yet been generally implemented (13). Because of the reaction of macroprolactin with most PRL assays, new assays that react only with monomeric prolactin are needed.

This study was undertaken to determine the prevalence of macroprolactin in patients with hyperprolactinemia in our region, and to determine the clinical and neuroradiological features of affected individuals. This may help improve the accurate evaluation of patients with hyperprolactinemia.

Materials and Methods

The study was performed in King Khalid University Hospital (KKUH), King Saud University, Riyadh, Saudi Arabia. PRL was measured using an electrochemiluminescence immunoassay (Modular Analytics E170 [Elecsys module] analyzer, Roche Diagnostics, Indianapolis, IN). The reference range was 86-324 mU/L in men and 102-496 mU/L in women; the intraassay coefficient of variation (CV) and interassay CV were 0.8% and 1.8% respectively. Approval for laboratory studies and clinical review was obtained from the ethics committee of KKUH.

Over a period of 12 months, from September 2006, 156 consecutive serum samples for a cohort of outpatients with elevated PRL (µ700 mU/L in women and µ500 mU/L in men) were subjected to polyethylene glycol (PEG) precipitation test to detect the presence of macroprolactin (14). PEG precipitation has been validated as a technique for detection of macroprolactin with the Elecsys PRL assay (15). A total of 200 µL of serum was added to 200 µL of a 25% solution of PEG (molecular weight 6000 kDa). After mixing and centrifugation, the PRL concentration was measured in the supernatant. Recovery was calculated based on the original serum value. Recovery ≤40% was classified as predominantly high molecular weight form (macroprolactinemia). Reproducibility of the PEG precipitation test was evaluated in ten different serum samples, studied five times each, in different assays and on different days. The intraassay and interassay CV of the PRL assay following PEG precipitation were 2.6% and 4.3% respectively. The hospital records of subjects with macroprolactinemia were reviewed retrospectively. Data on presenting symptoms and drug history; total PRL and macroprolactin concentration, neuroimaging studies, and subsequent management and follow-up were recorded.

Statistical analysis

Values are reported as mean±standard deviation (SD). Statistical analysis for the comparison of PRL values were performed with unpaired t-test. A P value <0.05 was considered statistically significant. Data were analyzed using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographic and laboratory data

A total of 156 subjects with hyperprolactinemia were studied; mean age was 32.2 (range 7-72) years, and 18 were males (11.5%). Of the 156 subjects, ten (6.4%) had a PRL recovery of ≤40% after PEG precipitation, indicating significant macroprolactinemia. In patients with significant macroprolactinemia, biochemical hyperprolactinemia was caused entirely by macroprolactin. The mean PRL level of those with macroprolactinemia was 760.9±185.2 mU/L (median, 716 mU/L). These PRL levels were not significantly different (P=0.11) from those observed in the remaining 146 patients (88.5%) who had hyperprolactinemia with confirmed predominance of the monomeric form (mean PRL levels of 1557.9±1587 mU/L, median, 962 mU/L).

Clinical features, neuroimaging, and dopamine agonist treatment

Table 1 shows clinical features, neuroimaging results, and presence of dopamine agonist therapy for the ten patients with macroprolactinemia. None presented with galactorrhea. In patients who underwent neuroimaging, magnetic resonance

Table 1. Clinical, biochemical, and radiological features and therapy with dopamine agonist (s) for 10 patients with macroprolactinemia

Patient	Presentation	Basal PRL (mU/L)	Post-PEG PRL (mU/L)	Pituitary Imaging	Therapy with Dopamine agonist (s)
47 M	Infertility	536	209	Normal	Yes
25 F	Oligo/amenorrhea	1036	245	Microadenoma	Yes
28 M	Infertility	511	169	Not done	No
33 M	Decreased libido and erectile dysfunction	641	253	Normal	No
28 F	Infertility	849	230	Not done	Yes
38 F	Oligo/amenorrhea and infertility	716	223	Normal	Yes
40 F	Oligo/amenorrhea and infertility	843	206	Microadenoma	Yes
52 M	Decreased libido and erectile dysfunction	716	230	Not done	Unknown
36 F	Oligo/amenorrhea	710	198	Normal*	Yes
24 F	Oligo/amenorrhea	1051	254	Normal	Yes

* Computed tomography scan was done.

imaging (MRI) was done in all but one case (in which computed tomography [CT] was performed instead). In five of six women who received dopamine agonist therapy, there was a reduction in the total PRL concentration. The remaining patient, who did not respond, was taking citalopram for depression. None of the patients has resumed normal menstrual cycle after dopamine agonist treatment. One man with infertility received dopamine agonist treatment, which did not affect his symptoms, and therapy was subsequently stopped.

Discussion

Measurement of PRL is commonly used to evaluate patients with reproductive disorders. Hyperprolactinemia is a common cause of menstrual disorders and can cause infertility both in men and women (16). Several studies have indicated that hyperprolactinemia may be secondary to the presence of macroprolactin, which is considered biologically inactive, a situation that may lead to unnecessary investigations and inappropriate management. This confusion is the result of detection of macroprolactin by the assay system used in the measurement of PRL. Currently used PRL immunoassays exhibit variable degrees of reactivity with macroprolactin. It is essential for those involved in the management of patients with hyperprolactinemia to be aware of the extent to which the assay system used in the measurement of PRL may detect macroprolactin. If the assay system used showed high reactivity with macroprolactin, an alternative procedure is needed. The aim of this study was to determine the prevalence of macroprolactin in patients with hyperprolactinemia in our region and to examine the clinical and neurological features of these patients. In this series, which is the first from Saudi Arabia, the prevalence of macroprolactinemia in the hyperprolactinemic population was 6.4%, a value considerably lower than that reported by the majority of screening studies from Europe and the United States (6,13). The most likely explanation for this difference is the low reactivity of the assay we used with macroprolactin compared to other assay systems. In fact, although all commercially available immunoassays used in the measurement of PRL may detect macroprolactin, a great variability among these assays has been reported (8). We used the Roche Elecsys Prolactin assay (Prolactin II), which uses two monoclonal antibodies and has been shown to have low reactivity with most forms of macroprolactin, as indicated in product literature.

Several studies have suggested that classical symptoms of hyperprolactinemia occur at lesser extent in patients with macroprolactinemia than in people with elevated monomeric PRL (11,12,17-19). In this series, however, all patients with macroprolactinemia presented with symptoms that could have been caused by hyperprolactinemia. This is in agreement with more recent reports, in which menstrual disorders, infertility, and galactorrhea were leading presentations to the diagnosis of macroprolactinemia (12). Our data therefore confirm that subjects with macroprolactinemia cannot be differentiated from hyperprolactinemic patients other than by measuring macroprolactin.

In the present study, pituitary adenomas were identified in two of seven patients with macroprolactinemia who underwent neuroimaging. This is higher than results found in larger series, which reported the presence of pituitary adenomas in approximately 20% of patients who screened positive for macroprolactin (11,20). Given the smaller sample population of this series and the fact that about 10% to 20% of the normal adult population may have abnormal pituitary imaging suggestive of pituitary adenoma (21), the presence of these abnormalities is probably incidental to the finding of macroprolactinemia, and thus it is likely that these findings represent nonfunctioning microadenomas. However, due to the reported association of pituitary abnormalities with macroprolactinemia, we suggest that neuroradiological imaging need to be done to rule out such abnormalities.

The observation that dopamine agonist therapy was prescribed to most patients in our series is consistent with previous retrospective reports. This allowed us to review how patients with hyperprolactinemia, not then identified to have macroprolactinemia, were managed (9,22). In addition to the finding that this treatment did not affect the underlying symptoms, the reduction in PRL concentration could mislead the treating physician that this treatment should be continued, and may delay making the correct diagnosis. Other possible reasons for symptoms, including polycystic ovary syndrome, drug therapy, and menopause need to be considered. Guay et al described six men with erectile dysfunction and very high levels of measured PRL. They had normal testosterone concentration and preserved nocturnal penile tumescence. Gel filtration chromatography showed a predominance of macroprolactin, and the diagnosis of psychological impotence was made. Four men had sex therapy and achieved normal sexual function after 2-4 months of counseling (23). Their report showed the importance of considering the diagnosis of macroprolactinemia in patients with sexual dysfunction refractory to dopamine agonist therapy.

Conclusions

In conclusion, macroprolactin is a cause of misdiagnosis and inappropriate treatment in patients with hyperprolactinemia. The present study further confirms the variability among different immunoassays in detecting the presence of macroprolactin; it also emphasizes the importance of understanding the interaction of PRL assay systems and detection of macroprolactin. For hyperprolactinemic sera, it is important to have an available validated method, such as the PEG precipitation test, to confirm the presence of macroprolactin. This will ensure appropriate management and follow-up for patients with this benign condition.

Acknowledgment

We thank the Medical Biochemistry Laboratory staff at KKUH for their help in performing PEG precipitation test.

References

1. Fraser IS, Zhuang GL. Polymers of prolactin and their clinical significance. Obstet Gynecol Surv 1990; 45: 515-20.
2. Suh HK, Frantz AG. Size heterogeneity of human prolactin in plasma and pituitary extracts. J Clin Endocrinol Metab 1974; 39: 928-35.
3. Cavaco B, Leite V, Santos MA, Arranhado E, Sobrinho LG. Some forms of big big prolactin behave as a complex of monomeric prolactin with an immunoglobulin G in patients with macroprolactinemia or prolactinoma. J Clin Endocrinol Metab 1995; 80: 2342-6.
4. Hattori N, Ikekubo K, Ishihara T, Moridera K, Hino M, Kurahachi H. Correlation of the antibody titers with serum prolactin levels and their clinical course in patients with anti-prolactin autoantibody. Eur J Endocrinol 1994; 130: 438-45.
5. Hattori N, Inagaki C. Anti-prolactin (PRL) autoantibodies cause asymptomatic hyperprolactinemia: bioassay and clearance studies of PRL-immunoglobulin G complex. J Clin Endocrinol Metab 1997; 82: 3107-10.
6. Hattori N, Ishihara T, Ikekubo K, Moridera K, Hino M, Kurahachi H. Autoantibody to human prolactin in patients with idiopathic hyperprolactinemia. J Clin Endocrinol Metab 1992; 75: 1226-9.

7. Schneider W, Marcovitz S, Al-Shammari S, Yago S, Chevalier S. Reactivity of macroprolactin in common automated immunoassays. Clin Biochem 2001; 34: 469-73.
8. Smith TP, Suliman AM, Fahie-Wilson MN, McKenna TJ. Gross variability in the detection of prolactin in sera containing big big prolactin (macroprolactin) by commercial immunoassays. J Clin Endocrinol Metab 2002; 87: 5410-15.
9. Suliman AM, Smith TP, Gibney J, McKenna TJ. Frequent misdiagnosis and mismanagement of hyperprolactinemic patients before the introduction of macroprolactin screening: application of a new strict laboratory definition of macroprolactinemia. Clin Chem 2003; 49: 1504-9.
10. Sadideen H, Swaminathan R. Macroprolactin: what is it and what is its importance? Int J Clin Pract 2006; 60: 457-61.
11. Hauache OM, Rocha AJ, Maia AC, Jr., Maciel RM, Vieira JG. Screening for macroprolactinaemia and pituitary imaging studies. Clin Endocrinol (Oxf) 2002; 57: 327-31.
12. Vallette-Kasic S, Morange-Ramos I, Selim A, Gunz G, Morange S, Enjalbert A, et al. Macroprolactinemia revisited: a study on 106 patients. J Clin Endocrinol Metab 2002; 87: 581-8.
13. Donadio F, Barbieri A, Angioni R, Mantovani G, Beck-Peccoz P, Spada A, et al. Patients with macroprolactinaemia: clinical and radiological features. Eur J Clin Invest 2007; 37: 552-7.
14. Vieira JG, Tachibana TT, Obara LH, Maciel RM. Extensive experience and validation of polyethylene glycol precipitation as a screening method for macroprolactinemia. Clin Chem 1998; 44: 1758-9.
15. Fahie-Wilson M, Brunsden P, Surrey J, Everitt A. Macroprolactin and the Roche Elecsys prolactin assay: characteristics of the reaction and detection by precipitation with polyethylene glycol. Clin Chem 2000; 46: 1993-5.
16. Luciano AA. Clinical presentation of hyperprolactinemia. J Reprod Med 1999; 44: 1085-90.
17. Fideleff HL, Ruibal G, Boquete H, Pujol A, Sequera A, Sobrado P. Macroprolactinemia in childhood and adolescence: a cause of asymptomatic hyperprolactinemia. Horm Res 2000; 53: 16-9.
18. Larrea F, Escorza A, Valero A, Hernandez L, Cravioto MC, Diaz-Sanchez V. Heterogeneity of serum prolactin throughout the menstrual cycle and pregnancy in hyperprolactinemic women with normal ovarian function. J Clin Endocrinol Metab 1989; 68: 982-7.
19. Miyai K, Ichihara K, Kondo K, Mori S. Asymptomatic hyperprolactinaemia and prolactinoma in the general population--mass screening by paired assays of serum prolactin. Clin Endocrinol (Oxf) 1986; 25: 549-4.
20. Strachan MW, Teoh WL, Don-Wauchope AC, Seth J, Stoddart M, Beckett GJ. Clinical and radiological features of patients with macroprolactinaemia. Clin Endocrinol (Oxf) 2003; 59: 339-46.
21. Molitch ME, Russell EJ. The pituitary "incidentaloma". Ann Intern Med 1990; 112:925-31.
22. Olukoga AO, Kane JW. Macroprolactinaemia: validation and application of the polyethylene glycol precipitation test and clinical characterization of the condition. Clin Endocrinol (Oxf) 1999; 51: 119-26.
23. Guay AT, Sabharwal P, Varma S, Malarkey WB. Delayed diagnosis of psychological erectile dysfunction because of the presence of macroprolactinemia. J Clin Endocrinol Metab 1996; 81: 2512-4.