Turkish Neurosurgery 2008, Vol: 18, No: 3, 223-227

The Importance of Macroprolactinemia in the Differential Diagnosis of Hyperprolactinemic Patients

Hiperprolaktinemik Hastaların Ayırıcı Tanısında Makroprolaktineminin Önemi

Celal BAĞDATOĞLU[1]
Özlem Tubay BAĞDATOĞLU[2]
Necati MUSLU[3]
Aslıhan KÖSEOĞLU[4]
Ahmet DAĞTEKİN[5]
Gürbüz POLAT[6]
Habibullah DOLGUN[7]
Mehmet Ali KARATAŞ[8]

[1,4,5,8] Mersin University, Neurosurgery, Mersin, Turkey
[2,3,6] Mersin University, Biochemistry, Mersin, Turkey
[7] Dışkapı Yıldırım Beyazit Education and Research Hospital, Neurosurgery, Ankara, Turkey

ABSTRACT

OBJECTIVE: Hypersecretion of prolactin (PRL) by lactotroph cells of the anterior pituitary may lead to hyperprolactinemia in physiological or pathological conditions. However, some of the patients may present with another cause of hyperprolactinemia, described by various authors as macroprolactinemia.

PATIENTS and METHODS: The clinical, radiological and biochemical assessment of 124 patients were carefully evaluated for differential diagnosis in light of the literature.

Macroprolactinemia was assessed by the polyethylene glycol (PEG) method in all of the patients, with high PRL level but without significant symptomatology, presenting to our clinic between 2004 and 2006.

RESULTS: The sera from 124 patients with hyperprolactinemia were screened for macroprolactinemia using the PEG method and macroprolactinemia was detected in 10 patients (8%). The average age of the patients was 35 years (range 23-46). Nine of the ten patients were female (90%) and one was male (10%). All of the patients had MRI. An intrasellar mass and stalk lipoma were found in three of the ten patients (30%).

CONCLUSIONS: In conclusion, macroprolactinemia should be taken into consideration as a probable cause of high serum prolactin levels to avoid repeated hormone assessments, neuroradiological examinations and unnecessary medical and surgical treatments.

KEY WORDS: Macroprolactinemia, Prolactin, Prolactinoma

ÖZ

AMAÇ: Prolaktinin (PRL) ön hipofiz laktotrop hücrelerinden artmış sekresyonu, fizyolojik ve patolojik hiperprolaktinemiye yol açabilir. Bununla birlikte, bazı hastalarda, çeşitli yazarlarca makroprolaktinemi olarak tanımlanan, hiperprolaktineminin bir başka sebebi görülmektedir.

YÖNTEM ve GEREÇ: 124 hasta, literatüre dayalı ayırıcı tanı amacıyla, klinik, radyolojik ve biyokimyasal olarak incelendi. 2004-2006 yılları arasında kliniğimize başvuran ve PRL düzeyi yüksek olup belirgin semptomu olmayan hastalar polietilen glikol (PEG) yöntemi ile makroprolaktinemi açısından değerlendirildi.

BULGULAR: Hiperprolaktinemili 124 hasta serumu makroprolaktinemi açısından PEG yöntemi ile çalışıldı ve 10 hastada (%8) makroprolaktinemi tespit edildi. Hastaların yaş ortalaması 35 ve yaş aralığı 23 ve 46 yıl idi. On hastanın dokuzu kadın (%90) iken bir tanesi erkekti (%10). Tüm hastaların MR incelemesi yapıldı. On hastanın üçünde (%30) intrasellar kitle ve stalk lipomu görüldü.

SONUÇ: Sonuç olarak, makroprolaktinemi, tekrarlanan hormon ölçümleri ve nöroradyolojik incelemelerin, gereksiz medikal ve cerrahi tedavilerin önlenebilmesi için, yüksek serum prolaktin düzeyinin olası bir nedeni olarak dikkate alınmalıdır.

ANAHTAR SÖZCÜKLER: Makroprolaktinemi, Prolaktin, Prolaktinoma

Received : 08.04.2008
Accepted : 18.07.2008

A report of this study has been presented in abstract form at the 18th congress of Turkish Neurosurgery, Antalya, Turkey
May 22-26, 2004

Correspondence address:
Celal BAĞDATOĞLU
Phone : +90 324 337 43 00
Fax : +90 324 337 43 05
E-Mail : cbagd@yahoo.com

INTRODUCTION

Hypersecretion of prolactin (PRL) by the lactotroph cells of the anterior pituitary may lead to hyperprolactinemia both in physiological or pathological conditions. Pregnancy and lactation are accepted as physiological causes, and lactotroph adenoma or hypothalamic-pituitary tumors are the pathological hyperprolactinemia conditions. Dopamine (D2) receptor antagonist drugs or hypothyroidism can be listed as other possible reasons. However, the cause of high serum levels of PRL cannot be explained in some cases, although an extensive clinical, hormonal, and neuroradiological work-up is performed (21). Such patients may be categorized as idiopathic hyperprolactinemia. A number of these patients may have radiologically undetected microprolactinomas. However, some may present with other causes of hyperprolactinemia, described by various authors (13, 24) as macroprolactinemia. This condition corresponds to the predominance of high molecular mass circulating PRL forms that have been postulated to represent PRL complexed with anti-PRL immunoglobulins (4,8,9,10,15,17). Human serum PRL appears in three forms including the biologically and immunulogically active monomeric PRL (little PRL, 23 kDa), biologically inactive dimeric PRL (big PRL, 50-60 kDa), and low activity tetrameric PRL (big-big PRL, 150-170 kDa) (20). The last two forms are also named macroprolactinemia (14).

While monomeric PRL (approximately 80% of all the PRL forms) causes clinical symptoms due to its in vivo effect, the other two forms may not because of their macromolecular forms. Macroprolactinemia may be diagnosed by gel-filtration chromatography (20) and polyethylene glycol (PEG) serum precipitation methods. PEG precipitation test is usually recommended in order to estimate the amount of the biological active monomeric PRL (5,6,7,16).

Ten patients were evaluated for macroprolactinemia out of 124 patients who had high PRL levels. The clinical, radiological and biochemical assessment of these ten patients were discussed in light of the literature.

PATIENTS and METHODS

Macroprolactinemia was assessed by the PEG method in all of the patients who presented to our clinic between 2004 and 2006 with high PRL levels and without significant symptomatology. The informative data is shown in (Table 1) including age, gender, symptomatology and radiological findings.

Table I: Characteristics and PRL levels of macroprolactinemic patients.

Patient	Age	Sex	T-PRL (ng/ml)	bb-PRL (ng/ml)	M-PRL (ng/ml)	Symptom	MRI
1	34	F	55,8	34	21,8	No	Normal
2	5	F	43,4	26,2	17,2	Headache	Normal
3	29	F	60,6	51,1	9,5	Headache	Normal
4	41	F	36,1	26,7	9,4	No	Normal
5	30	F	224	211	13	Fatigue, Headache	Stalk lipoma
6*	46	F	37,8	5,5	32,3	No	Normal
7	41	F	40,9	32	8,9	No	Intrasellar mass
8	44	F	44,0	27,1	16,9	Oligomenorrhea	Normal
9	28	M	94,5	84,2	10,3	Infertility	Normal
10	23	F	60,2	40,2	20	No	Normal
11*	38	F	30,6	1,6	29	Oligomenorrhea	Normal
12*	39	F	60,2	12,6	47,6	Headache	Normal
13	27	F	68	48	20	Headache	Intrasellar mass

F: Female, M: Male, T-PRL: Total PRL, M-PRL: Monomeric PRL, bb-PRL: big-big PRL

* The patients who were excluded from the study because of a recovery percentage over 50%.

PRL assay

PRL was determined by an electrochemiluminescence immunoassay (ECLIA) (Modular Analytics E170, Roche Diagnostics GmbH, Mannheim, Germany). PRL values were expressed as ng/ml of serum.

PEG precipitation test (6, 16)

The prolactin levels of all the patients were measured at the beginning of the study and then a PEG precipitation method was applied to the samples. Precipitation with PEG was carried out by adding equal volumes (500 μl) of serum to a 25% solution of PEG (molecular mass 6000 kDa, product no. 29577; Merck Ltd, Darmstadt, Germany). After mixing and centrifugation at 1500 xg for 30 minutes, the supernatant was removed for the next analysis. PRL concentrations were measured in the supernatant, without delay, by using the ECLIA method. The post PEG results were adjusted by a factor of two, to correct for dilution in the preparation of the PEG precipitation protocol. The result of the precipitation test was compared with those obtained from unprecipitated serum and accepted as the recovery percentage of PRL. Patients with a recovery less than or equal to 40% were considered as macroprolactinemia. Recovery percentages between 40%-50% were accepted as a gray zone, in which repetition of the study via another method was suggested. Recovery of more than 50% was expressed as a high proportion of monomeric PRL that was related with disease.

RESULTS

Thirteen of the 124 patients (10,4%) who were admitted to our clinic with high PRL serum levels were evaluated in terms of macroprolactinemia. However, the dominant component in three of the patients was found to be monomeric PRL. Therefore, these patients (6th, 11th, and 12th patients on table 1) were excluded from the study. It was found that the macroprolactin constituted most of the serum PRL level in other patients (10/13). The average age of the patients was 35, with a range of 23 to 46 years. Nine of the ten patients were female (90%) and one was male (10%). Three of the patients suffered from headache, one from oligomenorrhea, one from both headache and fatigue and one complained about infertility. The other four patients were found to be free of symptoms. Bilateral varicocele was found in a male patient suffering from infertility and was referred to the urology department. The vision, visual field, hormone profiles including thyroid hormones (T3-T4-TSH) and medical history of all the patients were evaluated. All of the patients underwent MRI. We discovered abnormal radiological findings in three of our patients (30%). A lipoma close to the stalk was found in one patient. The others had 3 mm (patient no 7) and 4 mm intrasellar masses (patient no 13) (Figure 1).

A decrease in the serum macroprolactin level was observed in patients who could be followed carefully. The follow-up of the patients regarding macroprolactinemia is continuing.

DISCUSSION

Antiprolactin antibody has been found in studies performed to reveal the etiology of macroprolactinemia (4,8,15,18). Several possibilities may be discussed for the cause of

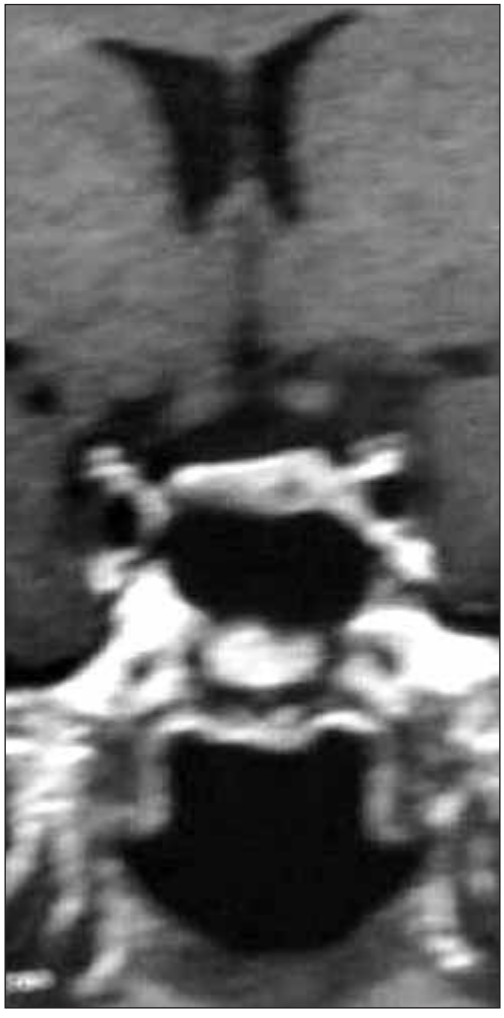

Figure 1: *Radiological finding of a patient: intrasellar mass.*

hyperprolactinemia in patients with anti-PRL auto antibodies including the prevention of the bound PRL filtration from the glomerules and less degradation in the target organs. A positive correlation was found between the titers of anti-PRL auto antibodies and the serum PRL levels, suggesting that the auto antibodies were the cause of hyperprolactinemia. The authors pointed out that the PRL suppressive effects of dopamine and bromocriptine were delayed and incomplete in patients with anti-PRL auto antibodies (10). Moreover, slower clearance of autoantibody-bound PRL compared to free PRL was demonstrated from the circulation (11).

In several investigations carried out, the symptoms of the patients, especially galactorrhea, appeared to be unclear despite the high prolactin level (10,12,16,22). We found that the macroprolactin ratio was 8% in our patients. However, in more comprehensive and serial investigations, this ratio was found to be between 15-36% (3,6,19,24). These high levels require more consideration of macroprolactinemia, especially for the patients whose hyperprolactinemic symptoms are rare. The reason why it was rare in our series might be either attributed to the rarity of the phenomenon or our possible underestimation of macroprolactinemia in our patients. However, discovering macroprolactinemia in 10 of the 124 patients shows us that this is not actually rare. Moreover, diagnosing it with a cheap and easy method is possible (22).

Male gender incidence was reported as very low in the majority of related studies (21, 23). On the other hand, a very high ratio of 50% was stated in another investigation (1).There is one male macroprolactinemic patient in our study group (10%). This ratio is in accordance with low incidence groups.

Macroprolactin, if present, is precipitated with 25% PEG, leaving decreased PRL values in the supernatant. Recovery of less than 40% is considered to be a significant level of macroprolactin present in the serum (6,16,19). This is a simple and inexpensive test that can easily be integrated into a laboratory practice. Gel filtration chromatography (GFC), the reference assay for macroprolactinemia, is used for detecting macroprolactin, although it is time-consuming and expensive compared with the PEG method (22). Another method, for example GFC, was required for checking the results in some cases for patients with a recovery of 40%-50%, (6,16).

The ratio of displaying an abnormal sella radiologically has been found to be 21% in a recent study (12). Such high false positivity shows the importance of diagnosing macroprolactinemia.

We have discovered abnormal radiological findings in three of our patients (30%) (patient no 5,7,13). However, we have not considered the rise of monomeric prolactin in the medical history of the three patients. We did not see any necessity for further treatment because we found macroprolactinemia in those patients. Macroprolactinemia does not require specific treatment (5,10,16) and no response to antiprolactinemic medicine has been discovered in studies that have been carried out (4,10). However, there is a reported study with a dopamine agonist medication which lowers the serum macroprolactin level (1).

In conclusion, macroprolactinemia should be taken into consideration as a probable cause of high serum prolactin level to avoid repeated hormone assessments, neuroradiological examinations and unnecessary medical and surgical treatments.

Acknowledgements

We wish to thank Assoc. Prof. Derya U. Talas, MD for his excellent support.

REFERENCES

1. Alfonso A, Rieniets KI, Vigersky RA: Incidence and clinical significance of elevated macroprolactin levels in patients with hyperprolactinemia. Endocr Pract May-Jun 12(3): 275-80, 2006
2. Bagdatoglu C, Ay A, Bagdatoglu OT, Ozer C, Polat G, Koksel T: The diagnostic importance of prolactin subgroups in patients with stalk mass. Acta Neurochir 147(2): 209-10, 2005
3. Bjoro T, Morkrid L, Wergeland R,Turter A, Kvistborg A, Sand T, Torjesen P: Frequency of hyperprolactinaemia due to large molecular weight prolactin (150–170 kD PRL). Scand J Clin Lab Invest. 55: 139 –147, 1995
4. 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 80: 2342–2346, 1995
5. Cavaco B, Prazeres S, Santos MA, Sobrinho LG, Leite V: Hyperprolactinemia due to big big prolactin is differently detected by commercially available immunoassays. Journal of Endocrinological Investigation 22: 203–208, 1999
6. Fahie-Wilson MN, Soule SG: Macroprolactinaemia: contribution to hyperprolactinaemia in a district general hospital and evaluation of a screening test based on precipitation with polyethylene glycol. Ann Clin Biochem. 34: 252–258, 1997

7. Fahie-Wilson MN, Brunsden P, Surrey J, Everitt A: Macroprolactin and the Roche Elecsys prolactin assay: characteristics of the reaction and detection by precipitation with polyethylene glycol. Clinical Chemistry 46: 1993–1995, 2000
8. Hattori N, Ishihara K, Ikekubo K, Moridera K, Hino M, Kurahachi H: Autoantibody to human prolactin in patients with idiopathic hyperprolactinemia. J Clin Endocrinol Metab 75: 1226–1229,1992
9. Hattori N, Ikekubo K, Ishihara K, Moridera K, Hino M, Kurahachi K: Effects of anti-prolactin autoantibodies on serum prolactin measurements. Eur J Endocrinol 130: 434–437,1994
10. Hattori N, Ikekubo K, Ishihara K, Moridera K, Hino M, Kurahachi K: Correlation of the antibody titers with serum prolactin levels and their clinical course in patients with anti-prolactin autoantibody. Eur J Endocrinol 130: 438–445,1994
11. Hattori N, Inagaki C. Anti-prolactin (PRL) autoantibodies cause asymptomatic hyperprolactinemia: Bioassay and clearance studies of PRL-immunoglobulin G complex. J Clin Endocrinol Metab 82: 3107–3110,1997
12. Hauache OM, Rochat AJ, Maia ACM, Maciel RM, Vieira JG: Screening for macroprolactinemia and pituitary imaging studies. Clinical Endocrinology 57 327–331, 2002
13. Jackson RD, Wortsman J, Malarkey WB: Macroprolactinemia presenting like a pituitary tumor. Am J Med 78: 346–350,1985
14. Schepper JD, Schiettecatte J, Velkeniers B, Blumenfeld Z, Shteinberg M, Devroey P, Anckaert E, Smitz J, Verdood P, Hooghe R, Hooghe-Peters E: Clinical and biological characterization of macroprolactinemia with and without prolactin–IgG complexes. Eur J Endocrinol 149(3): 201-7, 2003
15. Leite V, Cosby H, Sobrinho LG, Fresnoza MA, Santos MA, Friesen HG: Characterization of big, big prolactin in patients with hyperprolactinemia. Clin Endocrinol (Oxf) 37: 365–372,1992
16. Leslie H, Courtney CH, Bell PM, Hadden DR, McCance DR, Ellis PK, Sheridan B, Atkinson AB: Laboratory and clinical experience in 55 patients with macroprolactinemia identified by a simple polyethylene glycol precipitation method. Journal of Clinical Endocrinology and Metabolism 86(6): 2743–2746, 2001
17. Lindstedt G: Endogenous antibodies against prolactin: a "new" cause of hyperprolactinemia. Eur J Endocrinol 130: 429–432,1994
18. Lira DP, Reyes GD, Hernandez IC, Apolinar LM, Favela FB, Miranda AL: Frequency of macroprolactinemia due to autoantibodies against prolactin in pregnant women. J Clin Endocrinol Metab 86: 924–929, 2001
19. Olukoga AO, Kane JW: Macroprolactinaemia: validation and application of the polyethylene glycol precipitation test and clinical characterization of the condition. Clin Endocrinol. 51:119 –126, 1999
20. Smith CR, Norman MR. Prolactin and growth hormone: molecular heterogeneity and measurement in serum. Annals of Clinical Biochemistry 27: 542–550,1990
21. Sluijmer AV, Lappohn RE: Clinical history and outcome of 59 patients with idiopathic hyperprolactinemia. Fertil Steril 58: 72–77,1992
22. Vallette-Kasic S, Morange-Ramos I, Selim A, Gunz G, Morange s, Enjalbert A, Martin PM, Jaquet P, Brue T: Macroprolactinemia revisited: a study on 106 patients. J Clin Endocrinol Metab 87: 581–588, 2002
23. Vassilatou E, Schinochoritis P, Marioli S, Tzavara I: Macroprolactinemia in a young man and review of the literature. Hormones (Athens) 2(2): 130-4, 2003
24. Vieira JG, Tachibana TT, Obara LH, Maciel RM: Extensive experience and validation of polyethylene glycol precipation as a screening method for macroprolactinemia. Clin Chem. 44: 1758 –1759, 1998
25. Whittaker PG, Wilcox T, Lind T: Maintained fertility in a patient with hyperprolactinemia due to big, big prolactin. J Clin Endocrinol Metab 53: 863–866, 1981