Scripta Scientifica Medica, vol. 34 (2002), pp 51-54

HYPERPROLACTINAEMIA - ETIOLOGY, DIAGNOSIS AND TREATMENT

K. Hristozov, V. Nikolova, L. Koeva, P. Karatodorova

Clinic of Endocrinology and Metabolic Diseases, Prof. Paraskev Stoyanov Medical University of Varna

ABSTRACT

The problem of hyperprolactinaemia is a relatively new and the information regarding it is still controversial. The aim of the present investigation is to analyze a five-year experience of the Clinic of Endocrinology and Metabolic Diseases, Prof. Paraskev Stoyanov Medical University of Varna in this field. Eighty-six patients with high prolactin levels are analyzed: 81 females at a mean age of 32.4 years and 5 males at a mean age of 37.3 years. The patients are grouped as follows: 25 with prolactinomas, 23 with hypothalamic hyperprolactinaemia, 14 with empty sella syndrome, 6 with another hormone-secreting pituitary tumor, 4 with primary hypothyroidism and 5 with drug-induced hyperprolactinaemia. The diagnosis is based on clinical features, hormone levels, computer assisted tomography and magnetic resonance imaging. The main principles of treatment, their side effects and the results are discussed.

Key words: prolactinoma, hyperprolactinaemia, dopamin agonists, transsphenoidal adenomectomy, CT, MRI

INTRODUCTION

Hyperprolactinaemia is among the most common disturbances in hypothalamo-pituitary axis function. It occurs more frequently in females than in males. The incidence of hyperprolactinaemias in general population is found to be approximately 0.4%, whereas in female patients with reproductive problems it reaches 9-17%.

Hyperprolactinaemia comprises a heterogeneous group of disturbances characterized by high serum prolactin levels with or without hypogonadism and galactorhoea.

There are three main reasons known and used in the everyday clinical practice - physiological, pharmacological and pathological hyperprolactinaemia. Most often, the diagnostic and therapeutic interest is directed toward the third group which includes prolactinomas (incidence of 11-23% in the general population) followed by hypothalamic hyperprolactinaemia and some other pituitary diseases (acromegaly, Cushing disease, empty sella syndrome, etc.), thyroid gland pathology and some other nonendocrine diseases (5).

The treatment of hyperprolactinaemias is a very disputable problem and depends on the aims of the team of physician-patient and the ratio between the expected success and the potential risk of the chosen therapeutic option (4).

Address for correspondence:
K. Hristozov, Clin. of Endocrinology and Metabolic Diseases, Prof. P. Stoyanov Medical University of Varna, 55 Marin Drinov St, BG-9002 Varna, BULGARIA
E-mail: microeffect@nat.bg

The correctly chosen and well-conducted treatment should normalize the hormone hypersecretion, shrink the tumor size and correct the optic and other cranial nerve disturbances. If other parts of the hypothalamo-pituitary axis are also damaged by the primary process they should be normalized and, if possible, the need for chronic hormone-replacement therapy has to be prevented (8). With the introduction in the clinical practice of new very potent dopamin agonists the pharmacotherapy of hyperprolactinaemias became a very serious alternative of the neurosurgery and radiotherapy.

MATERIAL AND METHODS

For the period 1995-2001, 86 patients with hyperprolactinaemia are diagnosed, treated and followed-up in the Clinic of Endocrinology and Metabolic Diseases, Prof. Paraskev Stoyanov Medical University of Varna. Of them, 81 are females, aged between 17 and 56 years (mean age of 32.4 years) and 5 are males, aged between 23 and 60 years (mean age of 37.3 years). Prolactin serum levels are determined in all patients using immunoenzyme method with an upper limit of the normal range of 26ng/ml for females and of 18ng/ml for males. In addition, profile X-ray of the scull, computer assisted tomography (CT) and, in some cases, magnetic resonance imaging (MRI) of the brain and pituitary gland are done, visual fields and vision status are checked. Control serum levels of prolactin are measured annually and in cases where prolactinomas are present annual CT of the hypophysis is also performed.

RESULTS AND DISCUSSION

In our cases the clinical signs suggesting hyperprolactinaemia are as follows: galactorhoea in 71 patients (83%), hypogonadism in 48 (56%), headache in 23 (27%), and visual disturbances (bilateral hemianopsy) in 2 cases (2.3%).
Patients' distribution depending on the reason for hyperprolactinaemia is the following (Fig. 1): 25 with prolactinomas, 23 with hypothalamic hyperprolactinaemia, 14 with empty sella syndrome, 6 with another hormone-secreting pituitary tumor, 4 with primary hypothyroidism and 5 with drug-induced hyperprolactinaemia.

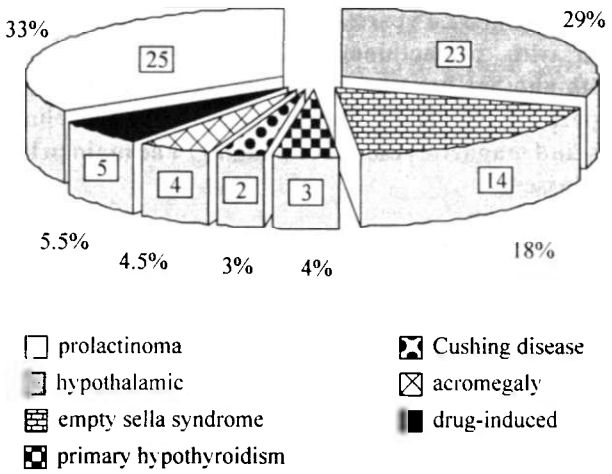

Fig. 1. Etiology of hyperprolactinaemia

From all patients with proved prolactinoma (N=23) in 8 cases macroadenoma is found (2 male and 6 female) and in 15 cases all of which are women microadenoma is found. The mean level of serum prolactin is 98 ±4.5ng/ml. In 7 patients with prolactinoma an operation was performed, two remain just under control without further treatment and in 14 cases a treatment with dopamin agonist (Bromocriptin of 2.5-10.0mg/d) was introduced. Since the therapeutic effect was insufficient and the side effects of Bromocriptin were pronounced in four of these cases Bromocriptin was replaced by Cabergoline (Dostinex) in an average dose of 0.5-1.0mg/week. The patients with low prolactin levels (25-40ng/ml) remain just under control.
In the group of macroadenoma patients (2 males and 2 females) an operation was performed - in 3 cases cranial adenomectomy and in one case transsphenoidal adenomectomy. In 3 patients with microadenoma transsphenoidal adenomectomy was done, too. After the operation complete radicalism was achieved in 2 patients, in 3 there was residual prolactin secretion, in one case residual tissue plus increased prolactin secretion and one case relapse of the tumor occurred. The ophthalmologic correction of the preoperatively registered bitemporal hemianopsy was achieved in 3 patients. During the first year of follow-up in 16 (71%) of all the patients with prolactinoma hormonal remission was achieved, in 6 cases (31%) there was a tumor shrinkage and in 65% of the patients with proved hypogonadism the gonadal function normalized (including 3 pregnancies).
As a reason for hyperprolactinaemia in 23 women hypothalamic dysfunction was found. This diagnosis was based on exclusion of any physiologic, pharmacologic or organic reason for high prolactin levels. In 14 cases (70%) hyperprolactinaemia was associated with gonadal dysfunction, in 7 of them with ovarian polycystosis. The serum levels of prolactin in all patients did not exceed 40ng/ml. A treatment with Bromocriptin was introduced in all patients from this group and in 20 cases (90%) hormonal levels were normalized, whereas gonadal function was restored in only 12 patients.
In 14 cases as a reason for high prolactin levels empty sella syndrome was found on CT of the pituitary gland. The mean levels of prolactin were of 51 +2.3ng/ml. Bromocriptin in a dose of 2.5-7.5mg/d normalized hormonal levels in 9 cases and gonadal function in 7 ones.
In 6 patients hyperprolactinaemia was found to be due to other pituitary tumors (4 cases with STH-producing adenomas and 2 with Cushing disease). In 2 of acromegalic patients hyperprolactinaemia was caused by cosecretion of prolactin and STH, whereas in the rest patients postoperative monosecretion of prolactin was found to be the reason. In ACTH-producing adenomas hyperprolactinaemia was diagnosed during the active phase of the disease. The introduced treatment with dopamin agonist achieved hormonal remission in all patients of the group and normalized the gonadal function in 3 of them.
In 4 patients with primary hypothyroidism (TSH 58.9 ±4.5mU/l; FT4 0.41.41 ±0.12ng/ml) caused by autoimmune thyroiditis the mean levels of prolactin were 69 ±3.4ng/ml. Clinically, in 2 of them there was a galactorhoea and hypogonadism. The levels of prolactin reduced, galactorhoea disappeared and hypogonadism was corrected when replacement therapy with levothyroxin was administered.
Drug-induced hyperprolactinaemia was found in 5 patients caused by Metoclopramide (2 cases), Dopegyt (1), Verapamil (1) and psychotropic drugs (1). The therapy with these drugs was interrupted afterward prolactin levels decreased. Only in one case (on a psychotropic drug) Bromocriptin was introduced simultaneously with the other medication afterward prolactin also normalized its levels.
Hyperprolactinaemia is one of the most common disturbances in the function of anterior hypophysis which leads to series of endocrine (infertility, osteoporosis) and neuroophthalmologic problems (5).
The most common clinical sign is galactorhoea which frequency is almost 80% in women with hyperprolactinaemia, whereas hyperprolactinaemia could be found in only about 50% in women with galactorhoea (1).
Our therapeutic aims in this series of patients were normalization of hormone secretion and, in the presence of

prolactinoma, tumor shrinkage and neuroophthalmologic correction. We also aimed at restoring the disturbed gonadal function and preventing, if possible, the need of permanent hormone replacement therapy. The treatment choice in the presence of prolactinoma depends on the tumor size and the serum level of prolactin. An operation was performed in 7 out of 23 patients with prolactinoma using the transsphenoidal approach in 3 patients with microadenoma and in one patient with macroadenoma but without suprasellar extension. In the other 14 cases the therapy was only conservative with dopamin agonists and in 12 patients the prolactin level restored to normal range as well as in 9 patients the tumor shrinkage was achieved. The reasons in some patients to perform an operation are various: not tolerated side effects of dopamin agonists such as hypotension, gastro-intestinal discomfort; the increase of prolactin secretion after stopping the drugs and in some cases financial problems. This was the case in 5 of our patients.

Unfortunately, despite the good results from the operative treatment it is not definitive sometimes. We found out that the normal prolactin levels immediately or soon after the operation do not testify always for definitive healing. Only in 2 out of 7 operated patients the prolactin level remained normal during the 2-year follow-up period. In the other 5 cases the operation was followed by treatment with Bromocriptin. In 2 cases residual tumor tissue was found out as a reason and in 3 cases an interruption of hypothalamo-pituitary connection could be discussed (9).

The other problem that could be discussed is about women with microprolactinomas, moderate hyperprolactinaemia without gonadal disturbances and galactorhoea. In most cases, microadenomas do not progress to macroadenomas because of their lower proliferative potential (7). That was also confirmed in our series of patients and in these cases we used to check the prolactin level every 6 months together with annual CT of the hypophysis.

The results from the surgical treatment of macroadenomas are not very promising. The effect from transsphenoidal operation of these tumors reaches hardly 30% and because of this there is a need for lifelong treatment with dopamin agonists (6).

Furthermore, the patients with macro- adenomas have greater risk for development of hypopituitarism due to intraoperative trauma or compression of the normal pituitary tissue by the tumor.

Hypothalamic hyperprolactinaemia (HH) called also idiopathic, functional or secondary is of great interest in the clinical practice. This is a diagnosis of exclusion, which requires a broad spectrum of laboratory and instrumental methods for exclusion of any other reason. Various factors could be discussed in HH etiopathogenesis such as disturbances in synthesis or secretion of dopamin from dorsomedial nucleus of hypothalamus (3), defects in secretion of other neurotransmitters such as GABA, cholecystokinin, VIP (10).

The patients with hypothalamic hyperprolactinaemia have lower mean prolactin levels in comparison to prolactinomas. The secretion of prolactin in case of HH is not autonomous and we could suppose that regulatory links between prolactin stimulating and inhibiting factors, on one hand, and lactotrophic cells in hypophysis, on the other hand, are relatively more intact in comparison to prolactinomas.

There is neither consensus, nor therapeutic algorithm concerning the indications for starting therapy with dopamin agonists in HH. Some publications state that if functional hyperprolactinaemia is not complicated with gonadal dysfunction and/or galactorhoea it does not require active treatment but only periodic control of prolactin levels. We conducted active treatment in 20 out of 23 patients with HH. Hormonal remission was achieved in all of them and in 12 the gonadal function was normalized.

The so-called empty sella syndrome commonly occurring in endocrinological practice does not exclude the coexistence of micro- or macroprolactinoma (2). In our patients we could succeed to control hyperprolactinaemia and tumor size by dopamin agonist administration.

In acromegalic patients galactorhoea with or without hyperprolactinaemia could result from co-secretion of STH and prolactin, lactotrophic effect of STH or interruption of pituitary stalk by the tumor (2). In such a case we controlled the high prolactin levels by dopamin agonists.

CONCLUSIONS

1. Women in reproductive age with microprolactinomas should be treated with dopamin agonists when a pregnancy is planned or they are in amenorhoea.
2. The surgical therapy (transsphenoidal adenomectomy) should be the treatment of choice when dopamin agonists' effect is not satisfactory or the side effects could not be tolerated.
3. In most cases hypothalamic hyperprolactinaemia does not require active treatment with dopamin agonists.

REFERENCES

1. Андреева, М., Ф. Куманов, А. Томова и съавт. Оценка на хипофизарната аденомектомия като метод на лечение на пролактиномите.- *Ендокринология*, 1998, № 1, 24-29.
2. Бозаджиева, Е., Л. Карагьозов. Тумори на хипофизата. София, Медицина и физкултура, 1987.
3. Bernardis, L. L., L. L. Bellinger. The dorsomedial hypothalamic nucleus revisited: 1998 update.- *Proc. Soc. Exp. Biol. Med.*, **218**, 1998, No 4, 284-306.
4. Dalkin, A. C., J. C. Marshall. Medical therapy of hyperprolactinemia.- *Endocrinol. Metab. Clin. North Am.*, **18**, 1989, No 2, 259-276.
5. Molitch, M. E. Pathologic hyperprolactinemia.- *Endocrinol. Metab. Clin. North Am.*, **21**, 1992, No 4, 877-901.

6. Molitch, M. E., M. O. Thorner, C. Wilson. Management of prolactinomas.- *J. Clin. Endocrinol. Metab.*, **82**, 1997, No 4, 996-1000.
7. Nishioka, H., H. Ito, J. Haraoka, A. Hirano. Growth potential of female prolactinomas.- *Surg. Neurol.*, **55**, 2001, No 4, 213-217.
8. Scamoni, C., C. Balzarini, G. Crivelli, A. Dorizzi. Treatment and long term follow-up results of prolactin secreting pituitary adenomas.- *J. Neurosurg. Sci.*, **35**, 1991, No 1, 9-16.
9. Veldman, R. G., M. Frolich, S. M. Pincus, J. D. Veldhuis, F. Roelfsema. Basal, pulsatile, entropic, and 24-hour rhythmic features of secondary hyperprolactinemia due to functional pituitary stalk disconnection mimic tumoral (primary) hyperprolactinemia.- *J. Clin. Endocrinol. Metab.*, **86**, 2001, No 4, 1562-1567.
10. Xu, R. K., X. M. Wu, A. K. Di, J. N. Xu, C. S. Pang, S. F. Pang. Pituitary prolactin-secreting tumor formation: recent developments.- *Biol. Signals Recept.*, **9**, 2000, No 1, 1-20.