PROLACTIN SECRETING PITUITARY ADENOMAS
- study regarding clinical, diagnostic and therapeutic aspects -

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ABSTRACT.
Hyperprolactinemia has different etiologic forms, among them, the prolactin-secreting pituitary tumors represent an important entity. In our study, we analyzed the clinical aspects, diagnostic procedures and therapeutic approach of 31 cases of prolactinomas (F/M ratio = 27/4) hospitalized in the Clinic of Endocrinology, County Hospital No. 1 Timisoara during the period 2000 - 2004. The study group was divided in two subgroups (by clinical, functional and imaging criteria): macroprolactinoma (13 cases; F/M = 9/4; age years = 36.69 ± 14.21); microprolactinoma (18 cases; F/M=18/0; age years = 31.55 ± 9.46). Prolactinomas represented 17.30% of cases from hypothalamic-pituitary pathology hospitalized in our clinic during the mentioned period. Anamnesis and clinical exam completed by hormonal assessment and imagistic investigations (CT/MRI) are essential for an accurate diagnosis. All the cases caused by the effects of hyperprolactinemia on hypothalamic-pituitary-gonadal axis and 5 patients with macroprolactinoma (F/M ratio = 2/3) presented tumor mass effect. The plasma prolactin levels were significantly higher (p < 0.00001) in patients with macroprolactinoma comparing with microprolactinoma cases. All the patients were treated with dopamine agonist drugs with very good response regarding the decrease of prolactin levels and tumor shrinkage (only one case didn’t show a normal prolactin level despite long term medical therapy associated with tumor disappearance, and despite the chang of dopamine agonist form). Four women with macroprolactinoma became pregnant after one year of treatment with bromocriptine and all of them reached the parturition without any event (continuing during the pregnancy the therapy with bromocriptine).

Key words: hyperprolactinemia, pituitary tumor, adenoma

ADENOAMELE PITUITARE SECRETANTE DE PROLACTINĂ - STUDIU CLINIC

Rezumat.
Hiperprolactinemia are diferite etiologii, prolactinomul reprezentând o entitate importantă. În studiul nostru au fost analizate aspectele clinice, metodele de diagnosticare și reușitele terapeutice la 31 de cazuri de prolactinom (F/B = 27/4) spitalizați în Clinica de Endocrinologie a Spitalului Județean nr. 1 Timișoara, de-a lungul perioadei 2000-2004. Grupul de studiu a fost împărțit în două subgrupe (după criterii clinice, funcționale și radiologice): microprolactinaome (13 cazuri F/B = 9/4; vârsta = 36,69±14,21), microprolactinaome (18 cazuri; F/B = 18/0; vârsta = 31,55±9,46). Prolactinoamele reprezintă 17,3 % din cazurile cu patologie hipotalamic hipofizară, spitalizate în clinica noastră de-a lungul perioadei menționate. Anamneza însoțită de examenul clinic complet au avut o importanță deosebită în diagnosticarea hiperprolactinemiei de cauză tumorală, în special la femeile adulte. Toate cazurile cauzate de efecte ale hiperprolactinemiei asupra axei hipotalamo-hipofizo-gonadale și 5 pacienții cu macroprolactinom (F/B = 2/3) au prezentat efecte tumorale masive. Nivele de prolactinemie serică au fost semnificativ mai ridicate (p<0,00001) la pacienții cu macroprolactinom comparativ cu cazurile cu microprolactinom. Toți pacienții au fost tratați cu medicamentele dopaminergice cu răspuns bun privind scăderea prolactinemiei și reducerea tumorală. Un singur pacient cu macroprolactinom tratat timp îndelungat cu agonisti dopaminergici nu a prezentat normalizarea prolactinemiei, în ciuda disparării formățiunii tumorale. Dintre paciențele cu macroprolactinom au prezentat sarcină după 1 an de terapie medicamentoasă, purtată la termen fără evenimente sub tratament cu bromocriptină.
INTRODUCTION

Hyperprolactinemia has different etiologic forms, among them an important entity is represented by prolactin (PRL)-secreting pituitary tumors.

The pituitary adenomas, their sizes, can be classified in two categories: microadenomas (tumor diameter < 10 mm) and macroadenomas (tumor diameter ≥ 10 mm).

The symptoms and the clinical signs induced by the PRL-secreting pituitary adenomas are caused by the hyperprolactinemia (affecting the gonadotropin pulsatility, presumably inhibiting GnRH and its lactogenic effect) and by the tumor mass effects (regarding macroprolactinomas).3,7

The suspicion of PRL-secreting tumors has to be raised in the following cases: delayed puberty; adult women with disturbances of the menstrual cycle, infertility, galactorrhea or men with erectile dysfunctions, infertility with/without gynecomastia and galactorrhea.

The aim of our study is to analyse the clinical, diagnostic and therapeutic aspects regarding hyperprolactinemia caused by pituitary tumors.

PATIENTS AND METHOD

The study group was represented by 31 cases with prolactinomas hospitalized in the Clinic of Endocrinology Timisoara during the period 2000 – 2004.

The patients were classified by the tumoral sizes in two groups, with micro- and respectively macroprolactinomas, using the following diagnostic methods:

- anamnesis and clinical exams (including ophthalmologic exam and the visual field assessment);
- hormonal assessments in the serum: prolactin (enzymatic assay - MEIA), TSH, FSH, LH, FT4, estradiol (chemiluminiscent assays), progesterone (enzymatic assay - MEIA), testosterone (chemiluminiscent assay), cortisol (competitive immunoassay);
- imaging techniques: skull X-ray (sella turcica); pituitary CT/pituitary MRI;

The results were analyzed statistically: Student’s test (significant threshold: p < 0.05) and Bravais-Pearson coefficient.

RESULTS AND DISCUSSIONS

The study group consisted 31 patients with PRL-secreting pituitary adenomas [age (years) = 33.71 ± 11.75; F/M = 27/4] hospitalized in the Clinic of Endocrinology Timisoara during the period 2000 – 2004, which represent a percentage of 19.30% from the patients with hypothalamic-pituitary pathology. (Figure. 1a, 1b)

Melmed S. and Kleinberg D. have observed an annual incidence of prolactinomas by 6/100,000, being the most frequent type of secreting pituitary adenoma.7

Figure 1a, b: The prevalence of prolactin-secreting pituitary adenomas in patients with hypothalamic-pituitary pathology (Clinic of Endocrinology Timisoara, period 2000 – 2004)
The study group was divided in two groups regarding the relation between prolactin serum level and adenoma size:

- cases with macroprolactinoma: $n = 13$;
  F/M ratio = 9/4; age (years) = $36.69 \pm 14.21$,
- cases with microprolactinoma: $n = 18$;
  F/M ratio = 18/0; age (years) = $31.55 \pm 9.46$.

Melmed S. and coworkers observed, in patients with microprolactinomas, a F/M ratio = 20/1, and in the patients with macroprolactinomas a F/M ratio = 1/1.  

The most relevant clinical aspects in patients with hyperprolactinemia caused by a pituitary tumor are revealed in Table I.

Melmed S. and Kleinberg D. found galactorrhea in about 50% of women with PRL-secreting adenomas and in 35% of men with prolactinomas, this is caused by a different sensitivity at the lactogenic effect induced by hyperprolactinemia.

Kleinberg D. and coworkers revealed the most frequent symptoms and clinical signs caused by hyperprolactinemia: menstrual cycle disturbances, erectile dysfunctions, galactorrhea, and osteopenia.

Different studies regarding the compressive effects induced by the tumoral mass revealed as most frequent symptoms the visual field impairment (bitemporal hemianopsia, superior bitemporal defects, decreased visual acuity) and headache. The hydrocephalus, ophthalmoplegia and temporal lobe seizures are rarely encountered.

Table I: clinical signs in patients with macro- and microprolactinomas

<table>
<thead>
<tr>
<th>Clinical Aspects</th>
<th>Macroprolactinoma</th>
<th>Microprolactinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galactorrhea (spontaneous/provoked)</td>
<td>10 cases</td>
<td>16 cases</td>
</tr>
<tr>
<td>Oligomenorrhea</td>
<td>-</td>
<td>8 cases</td>
</tr>
<tr>
<td>Secondary amenorrhea</td>
<td>9 cases</td>
<td>10 cases</td>
</tr>
<tr>
<td>Erectile dysfunctions</td>
<td>4 cases</td>
<td>-</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>1 case</td>
<td>-</td>
</tr>
<tr>
<td>Visual field impairment</td>
<td>5 cases</td>
<td>-</td>
</tr>
<tr>
<td>Intracranial hypertension</td>
<td>2 cases</td>
<td>-</td>
</tr>
</tbody>
</table>

Fig. 2b
The serum prolactin levels were significantly higher in patients with macroprolactinoma comparing with those who presented microprolactinoma. (Figure 2; Table II) Melmed S. and Kleinberg D. have observed a strong correlation between the tumor sizes and the prolactin serum levels and superior tumor sizes in men. A prolactin serum level higher than 200 ng/ml in correlation with tumor dimensions is strongly indicative of a PRL-secreting pituitary adenoma.\(^7\)

In a study which comprised 45 men and 51 women with prolactinomas Delgrange E. and coworkers found higher tumor sizes and a greater propensity to grow in men than in women. The authors consider that the correlation between the tumor sizes and the prolactin levels and superior tumor sizes in men. A prolactin serum level less than 200 ng/ml do not associate a prolactinoma (hyperprolactinemia occurs as a result of mass pressure on the pituitary stalk or portal circulation).\(^2\)

Table II: aspects of the hormonal parameters in the study group

<table>
<thead>
<tr>
<th>Hormonal Parameters</th>
<th>Macroprolactinoma</th>
<th>Microprolactinoma</th>
<th>Student’s Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin1 (ng/ml)</td>
<td>664.25 ± 694.84</td>
<td>205.17 ± 123.36</td>
<td>p &lt; 0.00001</td>
</tr>
<tr>
<td>FSH2 (mU/ml)</td>
<td>F: 2.61 ± 1.55</td>
<td>3.98 ± 1.95</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>M: 3.96 ± 1.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LH3 (mU/ml)</td>
<td>F: 1.67 ± 1.51</td>
<td>1.12 ± 0.69</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>M: 1.44 ± 1.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol4 (pmol/l)</td>
<td>62.41 ± 36.87</td>
<td>75.67 ± 44.62</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Progesterone5 (nmol/l)</td>
<td>2.48 ± 0.58</td>
<td>4.07 ± 11.14</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Testosterone6 (ng/ml)</td>
<td>1.77 ± 0.69</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

1- laboratory parameter: F = 1,39-24,2; M = 2,1-17,6;
2- laboratory parameter: F = follicular phase: 4- 15; ovulatory surge: 10-50; postmenopausal: 30-200; M = 0,9-15;
3- laboratory parameter: F = follicular phase: 4-30; ovulatory surge: 30-150; luteal phase: 4-40; postmenopausal: >40; M = 1,3-13;
4- laboratory parameter: follicular phase: 97,5-592; ovulatory surge: 685-1404; luteal phase: 120-738;
5- laboratory parameter: follicular phase: < 6; luteal phase: 6 - 64;
6- laboratory parameter: M = 2,86-15,11
The assessment of the hypothalamic–pituitary–gonadal function showed, in most cases, aspects of secondary hypogonadism. (Table II)

One case of macroprolactinoma (U.M., 28 years, gender male) associated pituitary insufficiency, and 4 patients (F/M = 1/3) PRL-secreting adenoma were diagnosed with TSH deficiency (secondary hypothyroidism).

The following significant correlations have been found:
- indirect correlations between the serum levels of the prolactin and estradiol ($r = -0.526; p < 0.05$) and between the serum levels of the prolactin and progesterone ($r = -0.908; p < 0.001$) in cases with macroprolactinoma (Figures: 3, 4);
- direct correlations between the serum levels of the estradiol and progesterone in patients with macroprolactinoma ($r = +0.754; p < 0.01$) and microprolactinomas ($r = +0.878; p < 0.00001$).

The patients with macroprolactinoma as well as those with microprolactinoma were treated with dopamine agonist drugs (bromocriptine, cabergoline). The doses were higher in patient with macroprolactinoma (bromocriptine → 30 mg/day) comparing with those who presented microprolactinoma (bromocriptine ~ 7.5 mg/day).
The cases who associated secondary hypothyroidism, or global pituitary insufficiency, respectively underwent also substitution therapy.

Under dopamine agonist therapy was observed in both groups a significant decrease in serum prolactin levels (p < 0.00001) a significant increase serum estradiol levels (p < 0.00001) and also the pituitary tumor shrinkage (pituitary CT/MRI). in women with PRL-secreting adenomas.

In patients who presented clinical signs of intracranial hypertension, visual field impairment and ophthalmoplegia was observed the remission of these aspects concomitant with the tumor shrinkage.

In women with PRL-secreting adenomas, the normal prolactin level obtained under the therapy was followed by the remission of the galactorrhea and by a normalized menstrual cycles (the substitution therapy with progestins could be interrupted, in most cases, when the prolactin reach the normal level).

The following aspects were revealed Melmed S. and Kleinberg D. as the optimal outcomes of treatment for a prolactinoma normalization of prolactin levels (and associated signs and symptoms) and complete tumor removal or shrinkage with reversal of the tumor mass effects.\(^7\)

Different studies showed that the medical therapy with dopamine agonist drugs has a great success in prolactinomas. These drugs shrinks prolactinomas by reducing tumor cell size, including cytoplasmic, nuclear and nucleolar areas. The efficacies were similar, in several studies, for bromocriptine, pergolide mesylate and cabergoline.\(^7,10,13\)

Four patients, diagnosed with macroprolactinoma in our clinic, became pregnant during a period of 1 year of medical therapy; they were treated during pregnancy with bromocriptine to prevent the tumor growth.

For adenomas Molitch M.E. revealed a risk of 25% to grow during pregnancy in women who were diagnosed with macroprolactinoma and who interrupted the treatment with dopamine agonist drugs during pregnancy. In consequence, in women with macroprolactinoma who want to become pregnant, it is recommended the surgical therapy or the maintenance of the treatment with bromocriptine during pregnancy (bromocriptine was not associated with teratogenic effects or with abortions or with premature deliveries).\(^3,9\)

The patient C.V., 56 years old diagnosed with macroprolactinoma (PRL = 1505 ng/ml) does not presented a normalization of the serum prolactin level (despite of the tumor shrinkage) under therapy with bromocriptină (30 mg/day).

Different authors observed patients with macroprolactinoma who showed difficulties in obtaining a normal prolactin serum level despite of the tumor shrinkage and the replacing of therapeutic drug.\(^7,11\)

None of the patients with macroprolactinoma from the study group did not undergo surgery, because the medical treatment with dopamine agonist drugs was successful.

The results of the total resection of macroprolactinomas are limited, the normalization of prolactinemia occurs in 32% of patients and the rate of recurrence after surgery is 19% cases.

Melmed S and Kleinberg D show the importance of surgical treatment of prolactinomas that have no response to dopamine agonist, in prevention of further tumor expansion. Surgery should be avoided in cases of extrassellar (without optic chiasm compression) expanding tumors because of the low success rate.

Radiotherapy is reserved for patients with PRL secreting macroadenomas who have persistant hiperprolactinemia and who have not respond to the surgical method or drugs. It lasts 3-8 years and has side effect –pituitary insufficiency. The method has a limited use due to its side effect.

**CONCLUSIONS**

1. Prolactinomas are the most common type of pituitary adenomas, accounting for about 36% of primary tumors, representing 19.30% of the total cases of pituitary pathology hospitalized in the Clinic of Endocrinology, County Hospital No. 1 Timisoara between the years 2000-2004.
2. Anamnesis and clinical exam completed by hormonal assessment and imagistic investigations (TC/MRI) are essential for an accurate diagnosis.
3. Five patients with macroprolactinoma (F/M = 2/3) presented tumor mass effect.
4. The plasma prolactin levels were significantly higher (p<0,00001) in patients to macroprolactinoma comparing with microprolactinoma cases.
5. All the patients were treated with dopamine agonists drugs with very good response regardind the decease of prolactin levels and tumor shrinkage (only one case didn’t show a normal prolactin level despite long term medical therapy associated with tumor disappearance).
6. Indications for treatment include the presence of the significant symptoms such as: disabling galactorrhea, amenorrhea and infertility, presence of visual field defect and cranial nerve pals, abnormal

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tests results such as detection of pituitary tumor, osteopenia or osteoporosis

7. One case didn’t show a normal prolactin level despite long term medical therapy associated with tumor disappearance and despite the chang of the dopamine agonist form.

8. Four women with macroprolactinoma became pregnant after one year of treatment with bromocriptine and all of them reached the parturition without any event.

REFERENCES: