Prolactin Secreting Pituitary Microadenoma: Results of Transsphenoidal Surgery After Medical Therapy With Dopamine Agonist

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Abstract: Medical therapy with dopamine agonist is very effective in controlling prolactin serum levels and it usually represents the first therapeutic choice for prolactin secreting pituitary adenomas. However, many patients present increase of prolactinemia after withdrawal of medical therapy which consequently should be taken for long time; other present intolerance to medical therapy; women with pregnancy need to withdraw dopamine agonists with consequent potential related problems: in these patients transsphenoidal surgery can be requested. The present study concerns the efficacy of transsphenoidal surgery in patients affected by microprolactinoma after treatment with medical therapy for different periods of time. Different postsurgical results were achieved in 2 groups of 24 (group 1) and 25 (group 2) patients affected by microprolactinoma who had taken medical therapy for a period of time respectively longer or shorter than 1 year. In summary, the authors observed in group 1 a rate of hormonal remission of 33.3% and an overall prolactinemia improvement with possibility of medical therapy withdrawal in 49.9% of patients. In group 2, the authors observed a rate of hormonal remission of 84% and an overall rate of improvement with no necessity of medical therapy of 92%. Therefore, the authors’ experience showed that the surgical option for the therapy of microprolactinomas should be indicated within 1 year from the beginning of medical therapy with dopamine agonist, to achieve a high rate of hormonal remission and possibility to withdraw medical therapy. The authors’ protocol for microprolactinoma treatment is presented.

Key Words: Dopamine agonists, microprolactinomas, pituitary gland, transsphenoidal surgery

METHODS

Two groups of 24 and 25 patients affected by microprolactinoma operated by transsphenoidal approach from 2000 through to 2010 in the same Institute (Department of Neurosciences, Neurosurgery, University of Rome Tor Vergata), by the first author (MFF) and the senior author (BF), are presented. Prolactin assay concerned exclusively the basal prolactin (ng/mL). In all patients pretreatment and preoperative basal prolactin level was higher than 100 ng/mL, and less than 200 ng/mL. Size of the microadenomas was included between 3 and 9 mm of maximum diameter; extension was purely intrasellar without invasion of cavernous sinus: this aspect was considered very important, because when cavernous sinus is invaded, in our experience the neurosurgeon should not take the risks of very important neurological deficits for the removal of intracavernous tumour component, but medical therapy and radiosurgery should be considered. All the patients present a clear magnetic resonance imaging (MRI) finding suggestive for microadenoma (Fig. 1). Only young patients were considered, between 17 and 48 years old (average 32.1 years). Postoperative results were evaluated according to the postoperative prolactin serum levels, which were the most important parameter to define clinical-hormonal remission, because postoperative MRI presented the common postsurgical findings that did not allow certainly identifying an eventual postoperative tumoral remnant. All the patients had performed previous medical treatment with dopamine agonist, cabergoline in 39 and bromocriptine in 10 patients. Patients who had performed medical therapy for more than 1 year and less than 1 year were included in group 1 and group 2 respectively. In all patients therapy with dopamine agonists was discontinued from 2 to 3 months before surgery.

Surgery was performed in all patients through a minimvasive submucosal microsurgical endoscope-assisted approach through 1 nostril. Suprasellar cisternal plane was not damaged in any patient so that no intraoperative cerebrospinal fluid fistula occurred. We selected a homogeneous cohort of patients with initial prolactin levels less than 200 ng/mL; in fact, it is known that high preoperative prolactin levels, over 200 ng/mL, are an important factor that inhibits hormonal remission, while our study was focused on assessing as well as possible the influence of the previous medical therapy alone on prolactin levels.

No significant differences were found in patients treated with cabergoline or bromocriptine.
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RESULTS

Histological examination revealed prolactin (PRL) adenoma cells in 44 patients (group 1: 22 patients; group 2: 22 patients), while PRL hyperplasia cells resulted in the other 5 (group 1: 2 patients; group 2: 3 patients). Prolactin controls were performed after 1, 3, and 6 months after surgery; PRL levels after 1 month were not significantly different from PRL controls after 3 and 6 months.

Group 1

Represented by 24 patients, 19 females and 5 males, of age between 18 and 45 years (average 34.8 years) who had taken medical therapy (cabergoline or bromocriptine in 18 and 6 patients respectively) for a period longer than 1 year. Two patients were submitted to transsphenoidal surgery after 16 and 19 months respectively because of intolerance to the drug; 12 other patients were operated after a period of medical treatment between 27 and 48 months, other 8 in a period between 5 and 7 years, and the 2 last patients after a period of medical therapy of 9 and 10 years respectively. Patients or endocrinologists requested surgery after prolonged time of medical therapy because of progression of hyperprolactinemia in 10 patients and need to withdraw cabergoline, because of onset of intolerance in 7 other, because of reduced therapeutic effectiveness in the last 7 patients. At surgery, in 20 (83.3%) patients the microadenoma presented fibrous consistence and it was not removable by suction; differently, it presented soft consistency and was removable by suction in 4 patients (16.7%) who had taken medical therapy respectively for 16, 27, 34, and 41 months.

Group 2

Represented by 25 patients, 22 females and 3 males, with age between 17 and 48 years (average 37.6 years), who had all taken medical therapy for a period shorter than 11 months: in 8 patients medical therapy had been suspended because of side effects occurring after few weeks, in the other 17 it was suspended in accordance with the endocrinologist and the patient, to achieve higher rate of success of surgical intervention and so withdrawal of medical therapy. At surgery, the microadenoma presented fibrous consistency in only 2 patients (8%).

DISCUSSION

Prolactin Secreting Pituitary Macroadenomas

Young patients affected by macroprolactinomas were not considered in this study because in these patients we propose transsphenoidal surgery, as other authors, because with this miniminvasive operation we can remove the tumor and decompress optic chiasm and the residual pituitary gland that could be (or could become) hypofunctioning because of the compression by the tumor, and in young women seeking fertility the problem of potential tumor enlargement during pregnancy can be avoided.

Table 1. Group 1 of 24 Patients

<table>
<thead>
<tr>
<th>Medical Therapy</th>
<th>Hormonal Remission</th>
<th>Implantation and Withdrawal of Medical Therapy</th>
<th>Improvement but Necessity of Medical Therapy</th>
<th>Improvement No Evidence of Total Resection at MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 2 y</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2 to 4 y</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5 to 7 y</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>9 to 10 y</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Results of transsphenoidal surgery after medical therapy with dopamine agonist for a period longer than 1.5 y.

MRI, magnetic resonance imaging.
Pregnancy

Surgery is very useful in female patients affected by prolactinomas who planned to have a pregnancy; in this condition, it is usually indicated to withdraw cabergoline, although some authors reported no side effects during pregnancy but these authors themselves reported the necessity of results on a larger number of pregnancies. Moreover, withdrawal is recommended by the production pharmaceutical company. During pregnancy and lactation, the adenoma could grow (as well as the physiologic growth of the pituitary gland during pregnancy), it could present hemorrhagic event with acute optic nerves compression or pituitary apoplexy or cranial nerve deficits with necessity of emergency operations.16

Analysis of Results

On the basis of our results, it is clear that, after surgery, hormonal remission occurred in 84% of group 2 patients, while it was achieved only in 33% of group 1 patients. Moreover, in group 2 patients we observed that persistence of hyperprolactinemia, even if improved, without necessity of taking again medical therapy because of absence of related symptoms, occurred in 3 of 4 patients (75%). Conversely, in group 1 only 4 of 14 patients (28.57%) who presented persistence of hyperprolactinemia had no necessity to restart medical therapy after surgery, although prolactin serum level improvement had occurred after surgery.

Moreover, it is evident that a longer presurgical medical treatment corresponded to a higher persistence of hyperprolactinemia (Table 1) and to a higher necessity to restart medical therapy. It is evident that protracted medical therapy modifies consistency of the adenoma which progressively becomes fibrous and difficult to remove.

Therapeutic Protocol for Microprolactinoma

Our results show that transphenoidal surgery allows very good results on hormonal remission when previous medical therapy has been taken for a period of time less than 1 year, and it presents progressive lower effectiveness when medical therapy has been protracted for a period longer than 1 year. So, our indications for the treatment of microprolactinomas in young patients plan to take medical therapy for a period of 6 to 8 months and to control serum prolactin levels after 1 and 4 months; afterward, 1 month after withdrawal of medical therapy, MRI and serum prolactin levels are performed: if reduction or disappearance of the microadenoma at the MRI and hormonal remission are evident, seriated serum prolactin levels control and MRIs are performed. If microadenoma is unchanged or increased, and there is again hyperprolactinemia, 2 strategies are indicated to the patients: the first one, suggested in our Institute, plans to perform transsphenoidal surgery with a very high rate of hormonal remission and very low rate of recurrence; the second strategy plans to continue medical therapy that probably should be performed for many years, and the patient is informed that a successive surgical operation, after 1 year and more, presents a progressive lower rate of hormonal remission.

In conclusion, the presented study showed that the surgical option for the therapy of microprolactinomas should be indicated within 1 year from the beginning of medical therapy with dopamine agonist, to achieve major rate of hormonal remission and possibility to withdraw medical therapy; hormonal remission after transphenoidal surgery is strictly related to the length of period of preoperative medical therapy; better results were achieved when dopamine agonists had been taken less than 12 months.

**REFERENCES**


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**TABLE 2.** Group 2 of 25 Patients

<table>
<thead>
<tr>
<th>Improvement and Withdrawal of Medical Therapy (Postop PRL Less Than 45 ng/mL)</th>
<th>Improvement but Necessity of Medical Therapy (Postop PRL Less Than 78 ng/mL)</th>
<th>Evidence of Total Resection at MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical therapy &lt; 1 y</td>
<td>21</td>
<td>3</td>
</tr>
</tbody>
</table>

Results after transphenoidal surgery in 25 patients affected by microprolactinomas who had assumed medical therapy less than 1 y.

MRI, magnetic resonance imaging.