

Therapeutic Options in Patients with Microprolactinoma

a report by

Marco Losa, Pietro Mortini, Paolo Ribotto and Massimo Giovanelli

Pituitary Unit, Department of Neurosurgery, San Raffaele Scientific Institute, Vita-Salute University

Prolactin (PRL)-secreting tumours represent the most common subtype of pituitary adenoma, usually causing menstrual disturbances and/or galactorrhoea in women of reproductive age and loss of libido or impotence in men. While large adenomas may also produce symptoms that are caused by compression of the surrounding nervous structures, microprolactinomas (i.e. tumours with a maximum diameter of less than 1cm) may cause symptoms that are only related to PRL excess. There is consensus that only patients with microprolactinomas who do not present clinically relevant symptoms may be followed up without treatment. Indeed, untreated microprolactinomas present a risk of further growth during follow-up of approximately 5%. On the other hand, the presence of symptoms of PRL excess, such as infertility, menstrual disturbances in women and loss of libido or impotence in men, is a clear indication for treatment of hyperprolactinaemia.

Therapy of PRL-secreting adenomas is circumscribed to medical therapy with dopamine agonists and surgery, whereas radiotherapy is reserved for the few patients who are neither controlled by medical nor by surgical treatments. On account of the excellent clinical results with dopamine agonists, medical therapy has become the preferred initial management of microprolactinomas. However, some drawbacks of medical therapy, such as the need for life-long treatment in the majority of patients, side effects limiting compliance by the patient and resistance of the tumour to dopamine agonists, have renewed interest in surgical treatment of microprolactinomas and refuelled controversy about the first-line therapy of these tumours. The aim of this paper is to review the pros and cons of medical versus surgical therapy of microprolactinomas.

Medical Therapy

Dopamine agonists, among which bromocriptine and cabergoline are the most frequently used, constitute the cornerstone of medical treatment of microprolactinomas. In female patients not wishing to become pregnant, it is also possible to initiate oestroprogestin preparations without dopamine

agonist therapy, because of the low risk of further PRL increase and tumour enlargement. However, the long-term effects of this strategy are still unknown and it is at present unclear whether hyperprolactinaemia *per se* may have negative effects in this group of patients.

Medical treatment should be initiated with low doses of drugs and then slowly increased until reaching normalisation of PRL levels or, at least, restoration of a normal gonadal function.

Results on PRL Levels and Tumour Size

Table 1 summarises the main results of treatment with dopamine agonists, mainly bromocriptine and cabergoline, in patients with microprolactinoma. All dopaminergic drugs effectively suppress PRL secretion in most patients; normalisation of PRL levels is usually achieved in more than 75% of cases. A large multicentre study in hyperprolactinaemic amenorrhoeic women has demonstrated that normalisation of PRL levels is more frequent with cabergoline (83.4%) than with bromocriptine (58.5%). The efficacy of cabergoline has later been confirmed by another open trial, in which normalisation of PRL levels was achieved in 92% of patients with microprolactinoma.

The effects of dopaminergic therapy on tumour size are less documented, especially for bromocriptine-treated patients. However, in cabergoline treatment, there is a 60–70% chance of tumour size reduction or even disappearance after repeated neuroimaging.

Side Effects of Dopaminergic Drugs

Side effects of dopaminergic drugs are common at the beginning of therapy (in approximately 60–70% of patients), but they are usually mild and subside in a few days. The most frequent complaints are nausea, vomiting, dizziness, orthostatic hypotension and constipation. However, suspension of dopaminergic therapy due to persistent or disturbing side effects is not



Marco Losa is the Clinical Co-ordinator of the Pituitary Unit at the San Raffaele Scientific Institute, Vita-Salute University, in Milan, Italy. He is a member of numerous societies, including the Endocrine Society, the European Neuroendocrine Association (Enea) and the Italian Society of Endocrinology (SIE). He is an author of more than 100 publications in peer-reviewed scientific journals and has been invited to hold lectures at national and international meetings. Dr Losa is also a manuscript reviewer for several medical journals, including *The Journal of Endocrinology & Metabolism*, *Clinical Endocrinology*, *European Journal of Endocrinology*, and *Journal of Endocrinological Investigation*.

Table 1: Results of Medical Treatment of Microprolactinomas

Normalisation of PRL levels	75–92%
Remission of hypogonadism	>90%
Reduction of tumour size	60–70%
Persistence of normal PRL levels for at least one year after withdrawal of dopaminergic drugs*	10–26% with bromocriptine 31–69% with cabergoline

*In patients who achieved normalisation of PRL levels during continuous therapy with dopamine agonists. Duration of therapy was a minimum of two years in most studies.

frequent and it seems less likely to occur with cabergoline than with bromocriptine. Indeed, in the aforementioned multicentre study, side effects severe enough to require withdrawal from the study were reported in 11.7% of the patients treated with bromocriptine and in 3.2% treated with cabergoline. The latter finding has been confirmed in another study, in which therapy with cabergoline was stopped because of side effects in 3.9% of the cases.

Withdrawal of Dopaminergic Drugs

A paramount issue is the possibility of discontinuing medical treatment without recurrence of hyperprolactinaemia. It has long been assumed that medical therapy should be continued indefinitely to maintain PRL levels in the normal range and prevent recurrence of hypogonadism. However, even in the absence of adequate treatment, a small portion of microprolactinomas may spontaneously regress, and similar findings have been described after stopping dopamine agonists. More than 20% of patients with microprolactinoma do not have recurrence of hyperprolactinaemia after discontinuation of bromocriptine therapy. Although a direct trial comparing bromocriptine with cabergoline is lacking, the results obtained with the latter drug seem even better. In one study, 31% of patients with microprolactinoma had normal PRL levels one year after discontinuation of therapy, whereas in another large study, 69% of 105 patients with microprolactinoma had no recurrence of hyperprolactinaemia two years after stopping cabergoline. These excellent results were obtained in a selected group of highly responsive patients who also had favourable tumour characteristics on magnetic resonance imaging (MRI).

Surgical Therapy

Surgical removal of the pituitary tumour is clearly indicated in patients with resistance or intolerance to dopamine agonists, whereas the decision to perform surgery as a first-choice therapy of microprolactinoma is more controversial. The main advantage of surgical as opposed to medical therapy is the possibility of inducing a definitive remission of hyperprolactinaemia, thus avoiding the need for chronic drug administration.

Moreover, in the long term, surgery seems to be more cost-effective than drug therapy. Nevertheless, two aspects of surgical therapy must be considered in detail: efficacy and safety.

Rates of Surgical Remission of Hyperprolactinaemia

In a recent series of patients operated upon for a PRL-secreting adenoma, the authors have reported remission of hyperprolactinaemia in 46 of 59 patients (78%) with a microprolactinoma. Similar findings have been reported in other recent surgical series. Previous therapy with dopaminergic drugs did not affect surgical results. Normalisation of hyperprolactinaemia is usually followed by regression of hypogonadism and headache. Moreover, even patients without normalisation of PRL levels can experience remission of symptoms. Recurrence of hyperprolactinaemia has been reported in a variable percentage of patients; this discrepancy is not easily explicable, because definition of relapse and length of follow-up are similar in the series. Most recurrences occur within four years after surgery.

Complications of Surgery

Mortality in 31 pooled surgical series was 0.27%. However, these data mainly include patients in the 1970s and 1980s, whereas recent and single-centre series show a 0% mortality risk in patients with microprolactinoma. Among the side effects of surgery, it is particularly important to consider the risk of hypopituitarism. In the authors' experience, preserved normal pituitary function was observed in all patients operated for microprolactinoma, with the exception of permanent diabetes insipidus in two of 59 cases (Losa). Similar data have also been reported by other authors. Only Turner et al. found a very high incidence of post-operative diabetes insipidus (15.6%) in their series.

Conclusions

Both medical and surgical therapy are very effective tools in the treatment of patients with microprolactinoma. Several arguments could be used to favour one or the other approach as the initial management of this condition. However, it is the authors' belief that the treating physician should openly and objectively discuss with the patient the advantages and disadvantages of medical and surgical treatment, respectively, allowing the patient to decide what is the best approach in her/his situation. ■

A version of this article, with references and an additional table, can be found in the Reference Section on the website supporting this business briefing (www.touchbriefings.com).