An ultrarapid prognostic index in microprolactinoma surgery

RÉGIS GUEU, M.D., PH.D., HENRI DUFOUR, M.D., FRANÇOIS GRISOLI, M.D., PHILIPPE JAQUET, M.D., YVES GUEU, M.S., JEAN PIERRE ROSSO, M.A., MURIEL MUNIER, M.D., VÉRONIQUE DECOUSTANZO, M.D., THIERRY BRUE, M.D., ALAIN ENJALBERT, PH.D., DOMINIQUE BEGOU, M.D., AND HÉRÉ ROCHAT, PH.D.

Laboratoire de Biochimie Faculté de Médecine Nord, Centre Nationale de la Recherche Scientifique, Marseille, France; Services de Neurochirurgie et d’Endocrinologie et Département d’Anesthésie-Réanimation, CHU Timone Adultes, Marseille, France; Collège H. Matisse, Nice, France; and Laboratoire de Biochimie, Hôpital Nord, Marseille, France

Object. Prolactinomas account for approximately 40% of pituitary tumors. If the tumor does not exceed 10 mm in its largest diameter (microprolactinoma), the chances of definitive cure as a result of surgery alone vary from 62 to 89% depending on the series. Until now, however, there was no mechanism to predict whether total excision of a tumor had been accomplished. To improve the chances of total excision, we compared the peri- and postoperative kinetics of circulating prolactin (PRL) in patients judged to be cured and those not cured.

Methods. The pre- and postoperative variations in blood PRL concentrations were determined using assays conducted at 10-minute intervals. Of the 36 patients included in the study, 27 were considered cured (resumption of a normal menstrual cycle within 6 months, PRL concentration at 9 days [mean ± standard deviation 2.5 ± 2.1 ng/ml] and 12 months [4.5 ± 2.2 ng/ml] after the operation < 10 ng/ml and normally stimulated by metoclopramide and thyrotropin-releasing hormone [TRH]). Nine patients were not cured (PRL 20 ± 15.7 ng/ml at 9 days after surgery, with no response to metoclopramide and TRH). The kinetics of PRL decrease in definitively cured patients were characterized by the following: 1) the initial slope of the curve decreased by at least 11% within the first 10 minutes after resection, and 2) immediate postoperative PRL concentrations were 20 ng/ml or less.

Conclusions. The measurement of the kinetics of PRL decrease during surgery allows the chance of gross-total resection to be successfully predicted less than 25 minutes after excision of the adenoma. Provided an ultrarapid assay is available (the test used in the present study took < 15 minutes), this prognostic index would be useful to make a decision to continue the surgical procedure when the initial PRL slope is judged to be insufficient. Its use may also be extended to other pituitary tumors such as somatotropic adenoma and basophilic adenoma (Cushing’s disease).

KEY WORDS • prolactinoma • neurosurgery • prognostic index

ROLACTINOMAS account for approximately 40% of pituitary tumors. Their frequency is approximately 10 to 20% in a standard (nonselected) population. Patients with these tumors have benefited from medical treatment with dopamine agonists, such as bromocriptine, which reduce tumor volume and return prolactin (PRL) secretion to normal concentrations in 80% of cases. However, surgery is widely used to avoid the side effects of this treatment and to handle bromocriptine-resistant prolactinomas. Advances in pituitary surgery involving use of the rhinoseptal route have led to a definitive cure in 62 to 89% of patients with microprolactinomas. However, there has been no early and reliable predictive index to ascertain whether surgery has been successful. Some factors, such as high preoperative concentrations of PRL, the presence of an invasive tumor, and the age of the patient at the time of surgery, have been reported to be factors in surgical failure. These factors, however, were not found to be implicated in a recent retrospective study involving more than 400 cases. To establish whether total excision had been achieved, we proposed to compare the peri- and postoperative kinetics of circulating PRL concentrations both in patients considered to be cured and those not considered to be cured.

Clinical Material and Methods

The study was performed during a 2-year period from 1995 to 1997. Thirty-six female patients between 17 and 47 years of age (mean age 27 ± 8 years standard deviation [SD]) who harbored a microprolactinoma were included in the study. The diagnostic criteria for microprolactinoma were: 1) a syndrome of amenorrhea or amenorrhea–galactorrhea; 2) a pituitary tumor visualized on magnetic resonance (MR) imaging that did not exceed 10 mm in its largest diameter; and 3) basal PRL concentrations higher than 20 ng/ml that were not stimulated by thyrotropin-releasing hormone (TRH) and metoclopramide hydrochloride. Exclusion criteria included: patients with a mixed adenoma; patients who had undergone previous
transsphenoidal resection for a PRL-secreting adenoma; and those who had undergone a previous craniotomy. Also excluded from the study were patients lost to follow-up review within 12 months postoperatively. Among the 36 eligible patients, 12 had been treated with dopaminergic medications (10 patients treated with bromocriptine [2.5–5 mg/day], one patient treated with lisuride [3 mg/day], and one patient treated with a combination of bromocriptine and lisuride [5 mg and 3 mg/day, respectively]), for a preoperative period lasting between 1 and 60 months (mean 17 months). Treatment was interrupted 1 to 10 months before surgery (mean 4 months). The other 24 patients were surgically treated at the outset without preliminary medical treatment.

All patients were informed of the aims of the study and the treatment modalities to be used, according to the Helsinki conventions, and consent was obtained from the ethics committee at Timone Teaching Hospital.

**Operative Procedure**

The same surgeon treated all patients via the rhinoseptal route. Each operation began within 15 minutes of 8:30 a.m. The duration between skin incision and the end of resection was 50 ± 5 minutes.

Regulation of anesthesia was performed in all cases by the same anesthesiologist. Premedication consisted of administration of 10 mg/kg morniflumate and 20 μg/kg lorazepam 30 minutes before induction of anesthesia, which was accomplished using propofol (2.5 mg/kg) and pancuronium bromide (8 mg/kg). After intubation, analgesia was initiated with 20 μg/kg phenoperidine and maintained with N₂O/O₂ (60%/40%). When the transpalatine retractors were installed, 20 μg/kg alfentanil was administered.

**Sample Collection**

Twenty-two samples (1 ml each) of venous blood from each patient were drawn through a small catheter into vacuum tubes containing ethylenediamine tetraacetic acid. The first sample was obtained before premedication (30 minutes before induction of anesthesia) and then every 10 minutes, starting 20 minutes before anesthesia induction and continuing until 80 minutes after extubation. The last sample was taken 24 hours after extubation. Finally one sample was collected 9 days postsurgery. Samples were immediately centrifuged at 2500 G for 10 minutes and the supernatants were frozen at −80°C before analysis.

**Assay Methods**

The blood samples were assayed for PRL by using enzyme immunoassay (Stratus II apparatus; Dade Behring International, Miami, FL) according to the manufacturer’s recommendations. This technique leads to an ultrarapid assay that can be performed in less than 15 minutes, including centrifugation. The sensitivity of the assay was 0.4 ng/ml and the intraassay coefficient of variation was 2%.

**Statistical Analysis**

The Mann–Whitney U-test was used to compare PRL
Ultrarapid prognostic index in microprolactinoma surgery

concentrations, adenoma sizes, and initial slopes between cured and uncured patients. An analysis of variance (ANOVA) was used to compare perioperative changes in hormone concentrations. The Spearman coefficient was used to analyze the correlation between adenoma size and PRL concentration on the one hand and between slopes and PRL concentrations on the other hand. Data are expressed as the mean ± SD.

Results

Postoperative follow up of patients lasted from 12 to 24 months (mean 18 months). The criteria for “cure” that we applied to patients included the reoccurrence of a normal menstrual cycle within 6 months after surgery and a circulating PRL concentration, evaluated at 9 days and 1 year postsurgery, that was less than 10 ng/ml and could be normally stimulated (≥ 2.5 × the basal level) by administration of TRH and metoclopramide.

Among the 36 patients who underwent surgery (Tables 1 and 2), 27 resumed a normal menstrual cycle. Their 9-day (mean 2.5 ± 2.1 ng/ml) and 1-year (mean 4.5 ± 2.2 ng/ml) postoperative concentrations of PRL were lower than 10 ng/ml and could be stimulated by metoclopramide and TRH. These patients are considered to be cured. In nine patients, the PRL levels remained high (mean 20 ± 15.7 ng/ml) and did not increase after metoclopramide or TRH stimulation. These patients were not considered to be cured.

There was a correlation between the largest dimension of the adenoma and preoperative PRL concentrations in cured (Spearman’s r = 0.66, p < 0.001) and uncured (r = 0.82, p < 0.05) patients. The correlation held when the entire patient cohort was considered (Fig. 1), but there was no significant difference in adenoma size between the two groups (p > 0.05; Table 2).

In patients who were not cured, preoperative basal PRL concentrations were significantly higher (152 ± 90 ng/ml) than in those considered cured (88.6 ± 44 ng/ml; p < 0.05; Table 2).

During the course of the operation, there was a significant decrease in PRL concentration 10 minutes after resection of the adenoma both in patients later considered to be cured (ANOVA, p < 0.05) and those who were not cured (p < 0.05; Fig. 2). However, the initial slope of PRL decrease, based on the sample obtained after resection of the adenoma (that is, the moment after which the surgeon no longer touches the sella turcica) and that obtained 10 minutes later (Fig. 2 and Table 2), was significantly lower for patients who were not cured (5.1 ± 2.4%) than for those who were cured (18.5 ± 6.4%; p < 0.001). This remained significant between 10 and 20 minutes after the end of resection (p < 0.001). Slopes calculated based on

Fig. 1. Scatterplot graph showing the correlation between adenoma size measured on MR imaging and preoperative PRL concentration in 36 women. Uncured patients are marked with square outlines. Spearman’s correlation coefficient is r = 0.57; p < 0.05.

Fig. 2. Graphs depicting the mean changes in plasma PRL concentrations during surgical resection of microadenomas in 36 patients. The concentrations of PRL are expressed in micrograms per liter (A) or in percentages of preoperative concentration (B). In the case of disease remission, the kinetics of PRL decrease during the first 20 minutes adhere to a model of 50% decrease in 30 minutes, followed by a model of 40% decrease in 30 minutes. In cases in which remission was not achieved, the decrease curve is situated above that of the model of a 40% decrease in 30 minutes. I = anesthesia induction; P1 = end of adenoma resection; P2 = 10 minutes after resection; P3 = 20 minutes after resection.
sampling at other times during surgery did not reveal such significant differences between the two groups.

Circulating PRL concentrations determined 120 minutes after resection were significantly higher in patients who were not cured \( (p < 0.001; \text{Table 2 and Fig. 2}) \).

Finally, there was an inverse correlation between the initial slope and the PRL concentration at 120 minutes \( (r = 0.45, p < 0.01) \) and between the initial slope and the PRL concentration 9 days postoperatively \( (r = 0.51, p < 0.05) \).

**Mathematical Study of the General Behavior of the Kinetics of PRL Decrease**

Figures 3 and 4 show examples of PRL release in successful and unsuccessful treatments.

**Modeling According to a 50% Decrease in Serum Concentration in 30 Minutes.** If \( C_0 \) is the PRL concentration at the end of the operation (initial concentration at time \( t = 0 \)), then the equation of the theoretical curve of changes in serum concentrations as a function of time \( t \), in minutes) is: \( C(t) = C_0 \left(e^{t/30}\ln(0.5)\right) \), where \( C(t) \) is the theoretical concentration at time \( t \), \( t/30 \) is the number of 30-minute "segments," and 0.5 is the ratio between serum hormone concentration after 30 minutes and serum hormone concentration at the end of the resection (1–50% = 0.5).

**Modeling According to a 40% Decrease in Serum Concentration in 30 Minutes.** Using the same parameters as those given for the 50% decrease, the equation is: \( C(t) = C_0 \left(e^{t/30}\ln(0.6)\right); \) (1–40% = 0.6).

It was found that all curves corresponding to a cure remained very close to the model by half-life at 30 minutes. After 20 to 40 minutes, the curves appeared to fit the model according a 40% decrease in 30 minutes. The results of all surgical failures spontaneously deviated, either numerically or by concavity, from the two models within the first 10 minutes after the end of resection.

**Limit Concentration for a Chance for Cure.** Modeling according to a 50% decrease in serum concentration in 30 minutes revealed an initial theoretical limit concentration (end of surgery = \( C_0 \)) beyond which there was no hope for a cure. Given that \( C(t) = C_0 \left(e^{t/30}\ln(0.5)\right) \), if as one of the indispensable criteria for definitive cure it is admitted that \( C(120) \) is less than 20 ng/ml, we thus have \( C(t) = C_0 \left(e^{120/30}\ln(0.5)\right) < 20 \) or \( C_0 < 20 \left(e^{-120/30}\ln(0.5)\right) \), that is, \( C_0 < 20 e^{-4}\ln(0.5) \) or \( C_0 < 320 \text{ ng/ml} \).

**Discussion**

The present study clearly shows that the peri- and postoperative decline in PRL levels differs depending on whether the patient’s disease is or is not in remission. Thus, regardless of peri- and postoperative PRL concentrations, the initial slope for all cured patients was at least equal to 11%, whereas the initial slope of those whose disease was not in remission was not in remission consistently remained lower than or equal to 8%. These results demonstrate that an initial slope of at least 11% indicates complete excision of the adenoma. This initial slope can be measured as early as 25 minutes after resection (including the 15 minutes needed for the PRL assay). Thus, in case the resection is subtotal, the surgeon may continue the procedure to achieve complete excision. Even though the number of patients whose disease is in remission is relatively low, the differences between slopes in the two groups are highly significant. In addition, in all patients whose disease was in remission the PRL level measured 120 minutes after resection was lower than 20 ng/ml. Considering the exponential shape of the curve, an initial PRL level that is too high indicates surgical failure. This limit concentration is approximately 300 ng/ml. This concentration had been implicitly assumed by several researchers who noted the impossibility of obtaining a cure by transsphenoidal surgery alone (probably because of the size of the adenoma) whenever preoperative PRL levels were higher than 300 ng/ml. Note also that, although patients whose disease was in remission generally had lower preoperative PRL levels.
plasma concentrations than those whose disease was not in remission, high preoperative PRL (although remaining < 300 ng/ml) is apparently not a factor in treatment failure. Thus, among the cases of treatment failure, three patients had preoperative PRL levels lower than 100 ng/ml (Cases 23, 24, and 31), whereas among the cases of remission, two patients had levels of 200 ng/ml (Cases 11 and 30).

The true halflife of PRL is measurable only in animals because, to ascertain halflife, radiolabeled PRL must be injected. However, our study suggests that the PRL halflife in patients whose disease was not in remission is longer than that in those whose disease was in remission, probably because the adenoma PRL secretory flux overflowed the PRL elimination. The adenoma resection normalized the “clearance” of PRL in the blood.

Surgical treatment for adenomas is indicated when there are severe side effects from medical treatment or if there is no response or only a partial response to medical treatment. Because the best surgical results are obtained in the absence of prior exposure to dopamine agonists, some authors recommend that surgery be performed at the outset. Feigenbaum, et al., reported that when postoperative PRL concentrations are lower than 20 ng/ml, the risk of incomplete excision is 26%, but when this level is lower than 5 ng/ml the risk is only 16%. These data are entirely consistent with our results, because the 9-day postoperative PRL concentrations in cases of remission were lower than 5 ng/ml and in no case were they higher than 10 ng/ml at 12 months after surgery.

The predictive perioperative study of the kinetics of decreases in PRL concentrations may be valuable for three reasons.

1) It leads to the early determination of whether complete excision of the tumor has been achieved and, if necessary, the surgery may be continued if the initial slope is judged too low. This is made possible by an ultrarapid assay that provides findings in less than 15 minutes.

2) The patient may be informed of the likelihood of successful excision immediately postoperatively, which may shorten hospitalization time, without the need to await the results of dynamic tests.

3) Finally, this approach could be extended to other pituitary tumors such as acromegaly or Cushing’s disease.

References

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Address reprint requests to: Régis Guieu, M.D., Ph.D., CNRS UMR 6065, Laboratoire de Biochimie, Faculté de Médecine Nord, Boulevard Pierre Dramard 13015, Marseille, France.