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Prediction of recurrence and remission within 3 years in patients with Cushing disease after successful transnasal adenomectomy

Elena Y. Nadezhdina[1] · Olga Yu. Rebrova[2,3] · Andrey Y. Grigoriev[1] · Oksana V. Ivaschenko[1] · Vilen N. Azizyan[1] · Galina A. Melnichenko[1] · Ivan I. Dedov[1]

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Abstract

Background Some laboratory and clinical features are associated with a probability of recurrence after transnasal adenomectomy for Cushing disease (CD). However, there is no consensus on a set of predictors. Rules for prediction of recurrence were not proposed earlier.

Aim To develop prediction model of recurrence/remission after successful neurosurgical treatment for CD.

Methods Retrospective single-site comparative study included 349 patients (52 men and 297 women) with a verified diagnosis of CD who underwent effective endoscopic transsphenoidal adenomectomy between 2007 and 2014. Clinical and laboratory parameters were evaluated. Laboratory tests were performed using immunochemiluminescent method. Time-to-event analysis and ROC-analysis were applied. Multivariate models were developed using logistic regression and artificial neural network (ANN).

Results Postoperative cortisol and ACTH levels and their combinations cannot be used for prediction of recurrence. ANN for prediction of recurrence within 3 years after successful surgery was developed. Input variables are age, duration of the disease, MRI data on adenoma, morning postoperative levels of ACTH and cortisol, output variable is binary (recurrence/remission). Predictive value for remission is 93%, 95% CI [89%; 96%], and predictive value for recurrence is 85%, 95% CI [71%; 94%]. Web-calculator based on the model is developed and free for use.

Conclusion Effective method for prediction of recurrence and long-term remission within 3 years after successful endoscopic transsphenoidal adenomectomy is proposed.

Keywords Cushing disease · Neuroendoscopy · Pituitary ACTH hypersecretion · Recurrence · Remission · Prediction · Neural network · Web calculator

✉ Elena Y. Nadezhdina
e.yu.nadezhdina@gmail.com

Olga Yu. Rebrova
o.yu.rebrova@gmail.com

Andrey Y. Grigoriev
medway26@gmail.com

Oksana V. Ivaschenko
leviv@rambler.ru

Vilen N. Azizyan
vazizyan@mail.ru

Galina A. Melnichenko
teofrast2000@mail.ru

Ivan I. Dedov
dedov@endocrincentr.ru

[1] Endocrinology Research Centre, 11 Dm. Ulyanova str., 117036 Moscow, Russia

[2] National Research University Higher School of Economics, 20 Myasnitskaya Ul., 101000 Moscow, Russia

[3] Pirogov Russian National Research Medical University, 1 Ostrovitianov str., 117997 Moscow, Russia

Introduction

Endoscopic transnasal transsphenoidal adenomectomy is a method of choice for the treatment of Cushing disease (CD) [1, 2]. Despite a high rate of remission (about 60–90%) [3–7], the rate of recurrence after successful primary transnasal adenomectomy with early postoperative remission varies from 10 to 47% [8–11].

Number of factors (gender, age, duration of the disease, postoperative levels of ACTH and cortisol, visualization of adenoma, size, and invasion of pituitary adenoma) were identified that had major or minor significance for recurrence prediction [3–5, 12–17]. However, there is no consensus on the significance of some factors and laboratory cut-off values. The methods for prediction of the disease recurrence or remission were not proposed either.

Thus, high rate of the recurrence provides a rationale for the investigation of the preoperative and postoperative predictors of the disease recurrence and the development of a method to predict the recurrence after successful neurosurgical treatment.

Materials and methods

Study design and patient population

Between 2007 and 2014, 498 patients with CD underwent transnasal adenomectomy in the Endocrinology Research Centre (Moscow, Russia). Among them, 402 (80.7%) patients achieved postoperative remission of adrenal insufficiency or normalized hormone levels (plasma ACTH and serum cortisol) in the early postoperative period (up to 10 days). Urinary free cortisol level and salivary free cortisol level were additionally measured in case of any uncertainty regarding postoperative remission.

The inclusion criterion in this study was a laboratory confirmed early postoperative remission. Patients with previous treatment (radiation therapy and/or neurosurgery) were excluded (53 patients). Overall, the retrospective study included 349 patients.

Endpoints and assessments

Parameters reviewed during the study included patients' demographics (gender and age), medical history (duration of the disease, previous treatment), the size of pituitary adenoma as assessed by MRI or multi-layer spiral CT, preoperative hormone levels including plasma ACTH and serum cortisol concentrations, morning and evening salivary free cortisol level, urinary free cortisol level, as well as postoperative hormone levels (plasma ACTH and serum cortisol concentrations, and, if required, evening salivary free cortisol level and urinary free cortisol level), and histological assessment of excised tumors. Hormone levels were measured by immunochemiluminescent method using automated Cobas 600 analyzer (Roche, France). Samples were collected within 2 months to 2 weeks prior to the surgery and on post-operative Day 1, and then, if values were normal, every other day until the discharge. If the values were lower than lower reference limit, glucocorticoid replacement therapy was started.

Time to recurrence or duration of remission was assessed.

Criteria of recurrence were applied as recommended by [14]:

(1) increased evening salivary cortisol level,
(2) no suppression of serum cortisol below 50 nmol/L (1.8 μg/dL) during the 1-mg dexamethasone suppression test,
(3) increased 24-h urine free cortisol level,
(4) increased concentrations and abnormal secretory rhythms of ACTH and cortisol,
(5) clinical recurrence of hypercorticism.

Any two criteria from items 1 to 3 indicated recurrence. Items 4 and 5 are optional as they present indirect evidence of CD recurrence. Death was not considered as a competing risk.

Statistical analysis

Median and quartiles for continuous variables and absolute and relative frequencies for categorical variables are presented as descriptive statistics. 95% Clopper–Pearson confidence intervals (CI) were calculated. Log-rank test was used in time-to-event analysis, and ROC-analysis was applied to find optimal cut-off values for continuous variables. Critical level of statistical significance P_0 was 0.05.

Multivariate models were developed using two approaches: logistic regression and artificial neural network (ANN). In both cases, recurrence within 3 years was used as a dependent binary variable. Accuracy of models was assessed by ROC-analysis and performance characteristics [sensitivity, specificity, positive and negative predictive values (PPV and NPV)] and 95% CI.

IBM SPSS Statistics v.18 (IBM, USA), Statistica v.13 (TIBCO, Inc., USA) software packages were used.

Results

The study included 349 patients (52 males, 297 females) aged 15 to 66 years with the duration of disease of 4 months to 22 years from the onset of first symptoms to diagnosis. Characteristics of enrolled patients are presented in Table 1.

Table 1 Characteristics of 349 enrolled patients

Parameter	Median and quartiles or counts and %
Ages (years)	38 [29; 48]
Gender (males, n, %)	52, 14.9
Duration of disease (years)	4 [2; 8]
Type of adenoma (n, %)	
Microadenoma (≤ 10 mm)	215, 61.6
Macroadenoma (> 10 mm)	93, 26.6
Not visualized	41, 11.8
Preoperative hormone levels	
Morning serum cortisol (nmol/L/μg/dL)	760 [582; 941]/28 [21; 34]
Evening serum cortisol (nmol/L/μg/dL)	629 [462; 836]/23 [17; 30], n = 344
Morning plasma ACTH (pg/mL)	78 [54; 112], n = 348
Evening plasma ACTH (pg/mL)	67 [46; 97], n = 338
Morning salivary free cortisol (nmol/L/μg/dL)	26 [17; 51]/0.9 [0.6; 1.8], n = 40
Evening salivary free cortisol (nmol/L/μg/dL)	19 [13; 31]/0.7 [0.5; 1.1], n = 160
Urinary free cortisol (nmol/24 h/μg/24 h)	1366 [874; 2398]/495 [317; 869]
Postoperative hormone levels	
Morning serum cortisol (nmol/L/μg/dL)	57 [38; 103]/2 [1; 4]
Evening serum cortisol (nmol/L/μg/dL)	99 [40; 222]/4 [1; 8], n = 123
Morning plasma ACTH (pg/mL)	8 [3; 16]
Evening plasma ACTH (pg/mL)	3 [1; 13], n = 149
Urinary free cortisol (nmol/24 h/μg/24 h)	115 [64; 176]/42 [23; 64], n = 24
Evening salivary free cortisol (nmol/L/μg/dL)	7 [3; 7]/0.25 [0.1; 0.25], n = 7

Fifty-eight of 349 patients experienced recurrence between 133 and 3234 days. Remission persisted in 291 patients with observation period from 5 to 4006 days (Fig. 1). 1-, 2-, 3-, 4-, 5-, 6-, and 7-year recurrence rates were 4.7%, 95% CI [2.2%; 7.2%], 10.5% [6.7%; 14.2%], 19.5% [14.4%; 24.5%], 20.1% [15.0%; 25.3%], 20.9% [15.6%; 26.3%], 25.2% [18.7%; 31.7%], 30.2% [22%; 38.3%], respectively. Thirteen cases of recurrence were observed during the first year and 47 cases during 3 years after surgery.

Impact of six variables (age, sex, duration of disease, type of adenoma, morning postoperative ACTH and cortisol) on time-to-recurrence was analysed. The values of continuous parameters were categorized by lower limits of reference intervals (123 nmol/L (4.5 μg/dL) for cortisol and 7 pg/mL for ACTH), 40 years for age, and 5 and 10 years for the duration of disease. No association was revealed between the time-to-recurrence and age, sex, duration of disease, type of adenoma, and significant association was demonstrated for morning cortisol and ACTH postoperative levels ($P < 0.001$, log-rank test, Figs. 2, 3).

As an auxiliary analysis, to find optimal cut-off values ROC-analysis was performed for these two hormone parameters in patients who had a recurrence within a 3-year period (n = 47) or remission for at least 3 years (n = 176) (Table 2).

Although both hormones demonstrate statistical significance in ROC-analysis, lower limits of 95% CI of AUC are rather poor. At the same time, lower limits of reference intervals, 123 nmol/L (4.5 μg/dL) for morning cortisol and 7 pg/mL for morning ACTH, were confirmed to be optimal cut-off values based on maximum sum of sensitivity and specificity.

Assessing the possibility to use hormone levels as predictors of recurrence, we analysed probabilities of recurrence within 1 and 3 years for cortisol and ACTH and their combinations (Table 3). These values are presented along

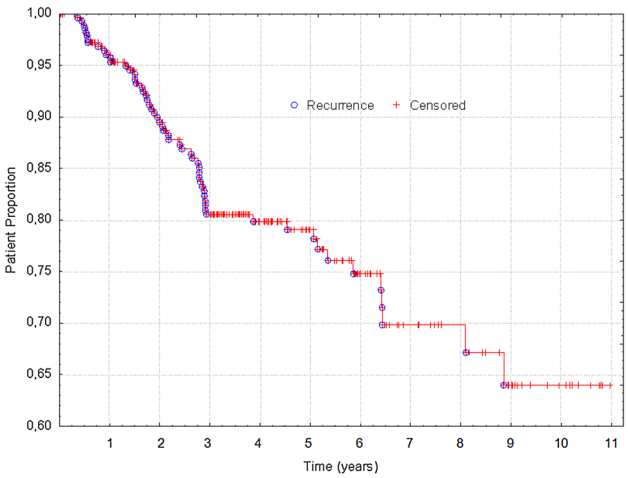

Fig. 1 Time-to-recurrence following successful neurosurgery for CD (n = 349)

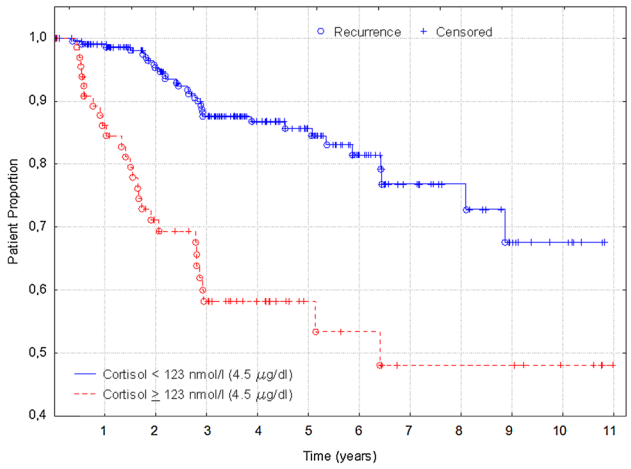

Fig. 2 Time-to-recurrence in the subgroups of patients based on the post-operative morning cortisol level (P < 0.001, log-rank test, n = 349)

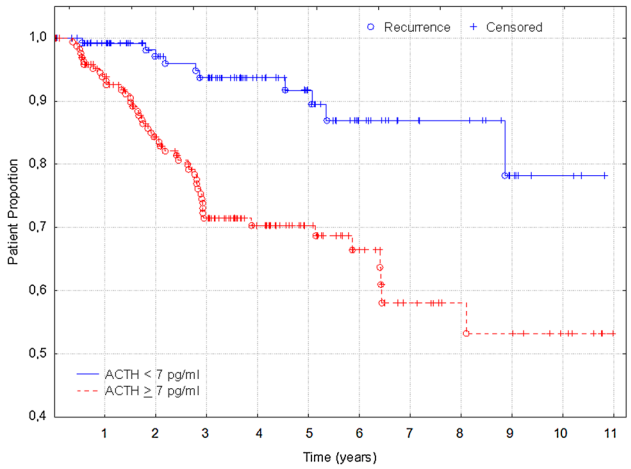

Fig. 3 Time-to-recurrence in the subgroups of patients based on the post-operative morning ACTH level (P < 0.001, log-rank test, n = 349)

recurrence because unacceptable imbalance of operational characteristics.

Therefore, next the multivariate analysis was performed in order to find a way to predict a 3-year recurrence. One-year prediction models were not developed because of small number of recurrence cases during the first year (n = 13).

In a multivariate analysis the number of observations has critical significance, so only six parameters without missing data were used as independent variables (inputs):

- sex (binary variable),
- age (years, continuous variable),
- duration of disease (months, continuous variable),
- type of adenoma (categorical variable),
- morning ACTH level in the early postoperative period (continuous variable),
- morning cortisol level in the early postoperative period (continuous variable).

The output binary variable was recurrence or remission within 3 years.

In order to generate and validate multivariate models, 219[1] cases (available by Year 3) were randomly allocated into training, control and test samples at the 70:15:15 ratio (155, 32 and 32 observations including 36 (23%), 6 (19%) and 5 (16%) recurrences respectively).

The attempts to use only ACTH and cortisol as independent variables were unsuccessful.

No statistically significant models were obtained by logistic regression analysis. Then ANNs of several topologies were developed—three- and four-layer perceptrons, radial basis functions, Bayes networks, and linear networks. The best results were obtained by three-layer perceptron developed using following methods: iteration Broyden–Fletcher–Goldfarb–Shanno 40 training algorithm, entropy error function, tanh hidden activation, and softmax output activation. The accuracy of prediction was

Table 2 Results of the ROC-analysis of hormone levels for prediction of recurrence within a 3-year period

Parameter	N	AUC	Standard error	P	Asymptomatic 95% CI for AUC	
					Lower limit	Upper limit
Morning serum cortisol, post-operative	223	0.706	0.047	< 0.001	0.613	0.799
Morning plasma ACTH, postop-erative	223	0.725	0.043	< 0.001	0.640	0.810

with OR, sensitivity, specificity, PPV, and NPV. Despite significant values of OR, neither hormone levels nor their combinations cannot be practically used as predictors of

[1] Data on 4 of 223 cases became available after the multivariate analysis was performed.

Table 3 Levels of cortisol and ACTH and their combinations as possible predictors of 1- and 3-year recurrence of Cushing's disease

	1-Year recurrence probability, 95% CI n = 262[a]	3-Year recurrence probability, 95% CI n = 223[b]
Cortisol		
≥123 nmol/L (4.5 μg/dL)	16% (8%; 28%), n = 62	45% (32%; 59%), n = 56
<123 nmol/L (4.5 μg/dL)	2% (0%; 4%), n = 200	13% (9%; 20%), n = 167
OR, 95% CI	12.6 (3.4; 47.6)	5.3 (2.7; 10.6)
Sensitivity, 95% CI	0.769 (0.469; 0.938)	0.532 (0.402; 0.654)
Specificity, 95% CI	0.791 (0.775; 0.800)	0.824 (0.789; 0.856)
PPV, 95% CI	0.161 (0.098; 0.197)	0.446 (0.338; 0.549)
NPV, 95% CI	0.985 (0.965; 0.996)	0.868 (0.832; 0.903)
ACTH		
≥ 7 pg/mL	8% (4%; 13%), n = 154	31% (23%; 40%), n = 134
< 7 pg/mL	1% (0%; 5%), n = 108	7% (3%; 14%), n = 89
OR, 95% CI	9.0 (1.2; 70.6)	6.1 (2.5; 15.1)
Sensitivity, 95% CI	0.923 (0.628; 0.996)	0.872 (0.749; 0.946)
Specificity, 95% CI	0.430 (0.414; 0.432)	0.472 (0.439; 0.491)
PPV, 95% CI	0.078 (0.053; 0.084)	0.306 (0.263; 0.332)
NPV, 95% CI	0.991 (0.955; 1.000)	0.933 (0.867; 0.971)
Cortisol and ACTH combinations		
Cortisol ≥ 123 nmol/ (4.5 μg/dL) and ACTH ≥ 7 pg/mL	19% (9%; 32%), n = 53	48% (33%; 63%), n = 48
Other combinations of cortisol and ACTH levels	1% (0%; 4%), n = 209	14% (9%; 20%), n = 175
OR, 95% CI	16.0 (4.2; 60.5)	5.8 (2.8; 11.8)
Sensitivity, 95% CI	0.769 (0.470; 0.938)	0.489 (0.364; 0.609)
Specificity, 95% CI	0.827 (0.812; 0.836)	0.858 (0.824; 0.890)
PPV, 95% CI	0.189 (0.115; 0.230)	0.479 (0.356; 0.596)
NPV, 95% CI	0.986 (0.967; 0.996)	0.863 (0.829; 0.895)

[a]87 of 349 patients dropped out without recurrence before end of Year 1

[b]126 of 349 patients dropped out without recurrence before end of Year 3

94% in the training sample, 87.5% in the test sample, and 84% in the control sample. ROC-analysis showed high efficacy of the model with AUC 0.912. The overall confusion matrix and operational characteristics of the ANN model are presented in Table 4.

The model performs over-diagnosis (i.e. predicts recurrence when there is actual remission) in 15% cases and under-diagnosis (i.e. predicts remission when there is actual recurrence) in 7% cases. So over-diagnosis is slightly higher than under-diagnosis. Such strategy is consistent with a high level of alertness for recurrence.

Thus, two rules for prediction can be proposed based on this model:

- "If the mathematic model predicts remission, the probability of remission for 3 years is 93% [89%; 96%]".
- "If the mathematic model predicts recurrence, the probability of recurrence within 3 years is 85% [71%; 94%]".

Because the ANN model is rather effective, web-based program application was developed, and it is available for free practical use at https://medcalc.appspot.com/eng_ver.

Table 4 ANN confusion matrix (n = 219)

	Observed values	
	Recurrence (n = 47)	Remission (n = 172)
Predicted values		
Recurrence (n = 41)	35	6
Remission (n = 178)	12	166
Sensitivity, 95% CI	75% [60%; 86%]	
Specificity, 95% CI	97% [93%; 99%]	
PPV, 95% CI	85% [71%; 94%]	
NPV, 95% CI	93% [89%; 96%]	
Overall accuracy, 95% CI	92% [87%; 95%]	

Discussion

In this study, the recurrence of CD after successful neurosurgery by 5 years of follow-up reaches 20.9%, 95% CI [15.6%; 26.3%]. The meta-analysis of 50 studies of CD presents 5-year follow-up recurrence rate varying from 0 to 55% with median 10% approximately [18]. Recurrence rate for CD is significantly less than for prolactinoma (30 studies), and more than for acromegaly (32 studies) when expressed as number of recurrences per total years at risk (0.023, 0.034, and 0.007 patients/years, respectively) [18]. The causes of different recurrence rates for different types of pituitary adenoma are not clear yet, while the recurrence of CD is rather high. Possible causes of relapse or lack of remission after transnasal adenomectomy are incomplete extirpation of the adenoma, tumor tissue that spreads into the cavernous sinus through the dura mater, and de novo tumor formation [19]. It is important to note that the invasion of the dura mater and, in particular, the medial wall of the cavernous sinus cannot be confirmed both by MRI and during tumor removal, and even the presence of small groups of cells can lead to persistence or relapse of the disease, regardless of the tumor size [19–21]. Some authors stress the importance of removing the so-called pseudocapsule of the tumor, which may contain tumor cells, and if removed, the frequency of prolonged remission of CD significantly increases [22–24]. Recurrence of CD is also associated with mutations in the gene encoding ubiquitin-specific protease 8 (USP8) [25]. This mutation was not found in other types of pituitary tumors [26, 27]. Adult CD patients with USP8 mutant tumours have a higher incidence of recurrence after transsphenoidal adenomectomy and shorter relapse free survival time [28].

The results of our study are consistent with the results of other studies with respect to the fact that morning ACTH and cortisol levels are statistically associated with recurrence and time-to-recurrence [4, 18, 29–31]. Predictors such as gender, age, duration of disease did not have any separate impact to the probability of recurrence as other authors describe [4, 18, 29, 31–33]. However we found that none of these hormones or combinations of their levels cannot be used as predictors due to poor operational characteristics. Other researchers either did not propose any approach to use these parameters as predictors. Therefore, we searched for potential rules for recurrence prediction using multivariate analysis. As a result, a highly effective mathematical model, ANN, was developed that offers an effective method of predicting recurrence within a 3-year period following transnasal adenomectomy in CD patients. Based on this model, web application (calculator) was developed for free use by doctors.

The limitations of the study are the following. Due to the retrospective design of the study, a historical bias cannot be excluded. The relatively low rate of occurrence of the events (recurrences) determines the need for long data collection period to obtain enough number of positive cases. Although this study uses data from 11 years of observations, this is still not quite enough to develop highly efficient multidimensional model. Also there is big amount of missing data because of retrospective design. Some of the patients originally scheduled for inclusion in the study could not be contacted, and therefore it was impossible to confirm or deny the remission of the disease during the 3-year follow-up period, which led to a restriction of the sample size.

We intent to continue the study in order to increase sample size and therefore to improve the mathematical model.

Conclusion

The effective mathematical model based on ANN for predicting recurrence of CD within 3 years after successful surgery was developed, and appropriate web based calculator is offered for free use.

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Compliance with ethical standards

Conflict of interest All authors on this manuscript have declared that they have no conflict of interest.

Ethical approval The study protocol was approved by the Local Ethical Committee of the Endocrinology Research Centre.

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