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Predictive factors for the recurrence of Cushing's disease after surgical treatment in childhood

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Abstract

Introduction: Cushing's disease (CD) is a rare cause of hypercortisolaemia caused by excessive adrenocorticotropic hormone (ACTH) excretion by a pituitary adenoma. Data on the predictive factors for the recurrence of the disease are limited in comparison with those for the adult population. The identification of the predictive factors for CD recurrence in patients after surgical treatment in childhood was the aim of the presented study.

Material and methods: A retrospective analysis of 26 CD patients, mean age at the time of diagnosis 13.46 years, treated at the Children's Memorial Health Institute (CMHI) in the years 1994–2018. Two time points were set at which the follow-up (FU) of patients was finished. The first time point (shorter FU, 24 patients) was set when the patients completed their treatment at the CMHI. The second time point (longer FU, 26 patients) was determined on the basis on the time when adult patients (previous CMHI patients) completed the author's questionnaire. In the case of the other patients (current CMHI paediatric patients and patients who did not respond to the questionnaire), the latest FU in this second time point was made during the last visit to the CMHI. The predictors of disease recurrence were evaluated by the construction of a logistic regression model and receiver operating characteristics.

Results: The average FU after transsphenoidal pituitary surgery (TSS) of 26 patients was 10.23 years (0.67–24.50). Recurrence of CD occurred in four out of 26 patients (15.4%) after an average time of 3.6 years (0.92–8.08) following definitive treatment. The results of the statistical analysis of potential predictive factors for CD recurrence were not conclusive, with no variables confirmed above the statistical significance threshold of $p < 0.05$. As regards the longer FU, two potential predictors: mean cortisol level at night ($p = 0.10$) and max. ACTH level after ovine corticotropin-releasing hormone (oCRH) test ($p = 0.10$), were the closest to meeting the assumed threshold of statistical significance.

Conclusion: Recurrence of CD may be diagnosed even a long time after its effective treatment.
It is possible that cortisol levels at night and ACTH values in oCRH test before TSS may be helpful to predict which patients may experience a recurrence after successful initial treatment. However, further studies on a larger sample are needed to confirm this hypothesis.
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Key words: *Cushing's disease; recurrence; predictive factors; transsphenoidal pituitary surgery*

Introduction

Cushing's disease (CD) is characterised by the excess production of adrenocorticotropic hormone (ACTH) by a pituitary corticotroph adenoma, which leads to hypercortisolaemia.

The first-line treatment is pituitary transsphenoidal surgery (TSS) [1]. Remission rates in the paediatric population are reported to be 45–95% [2–7], and recurrence rates are 6–27% in children after an initial remission [2, 6, 8]. Numerous researchers have attempted to determine the predictors for CD relapse. However, the results vary between studies, and currently no universal prognostic factor has been confirmed in all studies. Limited data indicate the potential prognostic factors of disease recurrence in children. Some predictive factors are common for both the paediatric and adult populations (such as: higher postoperative basal serum cortisol level and ovine corticotropin-releasing hormone [oCRH]-stimulated cortisol or ACTH levels, dural or petrosal sinus invasion, and no histopathological confirmation of pituitary corticotroph adenoma [9–12]), and others were reported only in children (e.g. older age at the onset of symptoms, younger age at the time of surgery, mutations in the *USP8* gene in the resected tumour tissue [5, 6, 13]). In this study we present the results of the analysis of a group of 26 patients after CD treatment in terms of the potential predictors for CD recurrence.

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Patients and methods

Patient inclusion

Twenty-nine consecutive paediatric CD patients who had undergone endocrine evaluation and/or pituitary surgery at the Children's Memorial Health Institute (CMHI) between 1993 and 2018 were initially included. The data of all patients had been previously reported [14]. The Institutional Bioethical Commission (48/KBE/2018) approved this study. Two patients with suspicion of recurrence and one patient with no follow-up (FU) after TSS were excluded, and for that reason the analysis of the predictive factors for CD recurrence was performed using the data of 26 patients in the long-term FU. Analysis based on the data only from CMHI patient medical records was performed in 24 patients because of no FU after TSS of two additional patients.

Preoperative evaluation

The investigation and diagnosis of CD was performed as previously described [14]. Patients with negative preoperative magnetic resonance imaging or an incomplete endocrine evaluation underwent bilateral inferior petrosal sinus sampling to determine the source of ACTH secretion [15]. Cortisol levels at night were defined as the mean values of two respective measurements: cortisol level at 00:00 h and 00:30 h. The oCRH test was performed as follows: a venous catheter was inserted the night before the test. Ovine corticotropin-releasing hormone was administered at a dosage of 1 μg/kg (max. 100 μg) of body weight at 08:00 h. Samples for cortisol and ACTH were taken 5′ before administration and at 0′, 15′, 30′, and 45′ after the administration of oCRH [16, 17].

Histological analysis

Resected tumour tissues were analysed as previously described [14].

Latest follow-up

Two time points were set at which the FU of patients was finished. The first time point (shorter FU, 24 patients) was set when the patients completed their treatment at the CMHI. The second time point (longer FU) was determined on the basis of the time when the adult patient (previous CMHI patient) completed the author's questionnaire. Answers to the questionnaire were obtained as previously described [14]. The patients were asked to indicate whether they had experienced a recurrence, whether they had a subsequent surgery, medical therapy, or pituitary radiotherapy, or were currently free of Cushing's syndrome. They were asked to indicate whether they were currently taking any medications. In case of other patients (current CMHI paediatric patients and patients who did not respond to the questionnaire), the latest FU in this second time point was made during the last visit to the CMHI. The recurrence of CD was defined as the presence of the biochemical features of CD, i.e. increased midnight cortisol, the lack of suppression of cortisol during LDDST, and increased 24 h urinary free cortisol values, which recurred after successful treatment that resulted in clinical remission. Long-term remission was defined as previously described [14].

Statistical analysis

The paired-samples T-Test was used to determine significant differences when variables had normal distribution. The Mann-Whitney test was used to compare groups with non-normal variable distribution. Significance was assumed if $p < 0.05$. Predictors of disease recurrence were evaluated by the construction of a logistic regression model and receiver operating characteristics (ROC). Variables analysed in this model were: sex, age at the time of the disease onset, age at the time of surgery, Δ between age at surgery and the disease onset, mean morning serum cortisol level before treatment, serum cortisol at night, max. serum ACTH level before treatment, max. serum ACTH level after oCRH stimulation test (before TSS), time of hydrocortisone (HC) substitution (after TSS), adenoma visualisation in magnetic resonance imaging (MRI), dural/petrosal sinus invasion, and adenoma in histopathological examination. Data were analysed using Statistica 13 PL.

Results

The mean time of observation of 24 patients (10 females and 14 males) during care at CMHI (shorter FU) was 3.87 years (0.17–10.17) from TSS. Three patients (12.5%) recurred during this time at an average time of 4.50 yrs. (1.75–8.08) from definitive treatment. The mean time of longer FU of 26 patients (12 females and 14 males) was 10.41 yrs. (0.67–24.50). Recurrence occurred in four of 26 patients (15.4%) at an average time 3.6 years (0.92–8.08) from definitive treatment. Three of these four recurred patients (75%) had hypocortisolism after TSS, and one (25%) patient had hypocortisolism after radiotherapy, which was used because biochemical remission after the second TSS was not achieved. Detailed characteristics of patients with recurrence were presented in the previous article [14].

Key characteristics of the variables used in the logistic regression for patients with and without CD recurrence are presented in Table 1. There was no significant difference between the patients with recurrence and the patients with long-term remission, regarding: height standard deviation score (SDS) and BMI SDS at presentation, age at the time of the disease onset, Δ between age at surgery and the disease onset, mean morning serum cortisol level before treatment, max. serum ACTH level before treatment, max. serum ACTH level after oCRH stimulation test (before TSS), time of HC substitution, height SDS, and BMI SDS at follow-up (Tab. 1). There were significant differences in age at the time of surgery ($p = 0.55$) and mean serum cortisol at night ($p = 0.10$).

Adenoma was visualised in MRI in 17/26 patients (65.4%). Two of the 26 patients (7.7%) presented with evidence of cavernous sinus invasion. None of these patients recurred. Histopathological examination confirmed a corticotroph adenoma in 20/26 (76.9%) patients. In two patients there were focal corticotroph hyperplasia and normal pituitary gland presented, respectively. Both patients were in remission at latest FU. In the remaining four patients there are no data on the result of histopathological examination (no data in patient medical records).

Predictive factors for disease recurrence

The median time of non-recurrence in the analysis with longer FU was 9.5 years (95% CI: 6.75–16.17) and 3.42 years (95% CI: 2.33–7.33) in the analysis with shorter FU (Fig. 1A and 1B).

The results of analysis of predictive factors for CD recurrence in two groups — with shorter and longer

Table 1. *The characteristics of patients with Cushing's disease (CD) recurrence (18% of patients) and patients with no recurrence (82% of patients)*

	Group A Patients with CD recurrence						Group B Patients with no CD recurrence						t-student test	Mann--Whitney test
	Count	Mean	Median	Min	Max	SD	Count	Mean	Median	Min	Max	SD	p	U
Height SDS at presentation	4	–1.41	–1.32	–2.47	–0.54	0.89	22	–1.82	–1.54	–4.04	–0.23	1.16	NS	
BMI SDS at presentation	4	1.92	1.89	1.51	2.39	0.37	22	1.24	1.34	–1.61	3.16	1.24	NS	
Age at the time of the disease onset [yrs]	4	9.55	10.10	5.50	12.50	3.06	22	9.96	10.78	4.33	16.00	2.69	NS	
Age at the time of surgery [yrs]	4	12.50	12.04	9.08	16.83	3.22	22	13.53	14.42	5.42	17.25	3.15	NS ($p = 0.55$)	
Δ between age at surgery and the disease onset [yrs]	4	2.95	3.17	1.13	4.33	1.37	22	3.57	3.21	0.82	9.08	2.44	NS	
Mean morning serum cortisol level before treatment [μg/dL]	4	30.47	26.58	22.65	46.08	10.86	22	28.30	24.03	11.70	79.82	15.63	NS	
Mean serum cortisol at night [μg/dL]	4	28.70	23.88	17.50	49.53	15.04	20	18.31	14.15	8.20	51.70	10.30	NS ($p = 0.10$)	
Max. serum ACTH level before reatment [pg/mL]	4	96.50	91.00	68.00	136.00	28.49	22	116.12	79.30	16.00	536.00	106.53		NS
Max. serum ACTH level after oCRH stimulation test (before TSS) [pg/mL]	3	96.33	95.00	48.00	146.00	49.01	18	253.61	143.50	17.60	1000.00	258.53		NS
Time of HC substitution [yrs]	4	3.79	3.08	1.00	8.00	3.16	21	7.61	3.25	0.00	24.33	7.74	NS	
Height SDS at follow-up	4	–0.96	–0.58	–3.36	0.68	1.71	22	–0.99	–1.09	–2.25	1.01	0.85	NS	
BMI SDS at follow-up	4	0.81	0.81	0.71	0.93	0.09	22	1.02	1.06	0.41	1.55	0.26	NS	

ACTH — adrenocorticotropic hormone; BMI — body mass index; HC — hydrocortisone; oCRH — ovine corticotropin-releasing hormone; SDS — standard deviation score; TSS — transsphenoidal pituitary surgery; HC — hydrocortisone; NS — not significant

FU — are presented in Table 2 and 3. It was checked whether there are variables differentiating patients with recurrence from patients without recurrence with sufficient statistical significance. No variables were confirmed above the statistical significance threshold of $p < 0.05$. As regards the longer FU, two factors: mean cortisol level at night and max. ACTH level after oCRH test, were closest to meeting the assumed threshold of statistical significance (Tab. 2 and 3). In the analysis, the increase of mean cortisol level at night increased the likelihood of recurrence, and the increase of max. ACTH level after stimulation in the oCRH test reduced the likelihood of recurrence. Adding interactions between variables (e.g. interaction: surgery age*max. ACTH, MRI result*time of HC substitution) did not make the logistic regression model significant at the level of statistical significance $p < 0.05$. A larger number of patients would be required to test the parameters mentioned above at this level of statistical significance.

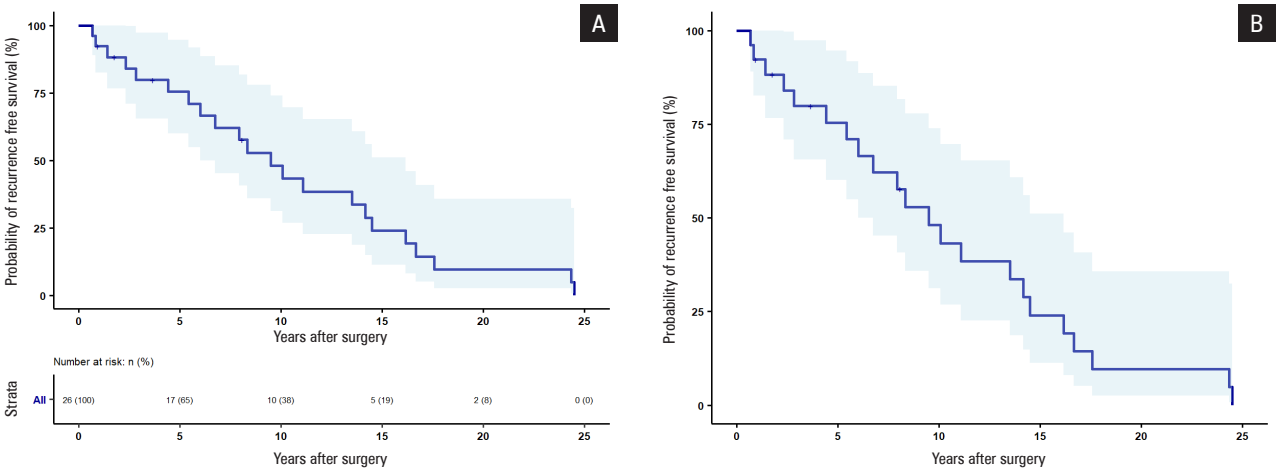

Figure 1. *Kaplan-Meier plot of recurrence-free survival in patients with remission of Cushing's disease (CD) after transsphenoidal pituitary surgery (TSS);* ***A.*** *Follow-up (FU): 10.23 years (0.67–24.50);* ***B.*** *FU: 3.87 years (0.17–10.17)*

Table 2. ***Results of the logistic regression model in groups with shorter and longer follow-up (FU)***

	Logistic regression ratio	Standard error	Wald test	95% CI bottom	95% CI top	p
Shorter FU						
Mean cortisol at night	0.240	0.154	2.435	–0.061	0.542	p = 0.11
Max. ACTH level after oCRH stimulation test (before TSS)	–0.019	0.012	2.466	–0.043	0.05	p = 0.11
Longer FU						
Mean cortisol at night	0.1509	0.0994	2.31	–0.0439	0.3456	p = 0.10
Max. ACTH level after oCRH stimulation test (before TSS)	–0.0123	0.0080	2.37	–0.0279	0.0034	p = 0.10

ACTH — adrenocorticotropic hormone; oCRH — ovine corticotropin-releasing hormone; TSS — transsphenoidal pituitary surgery; CI — confidence interval

Table 3. ***Statistical analysis — odds ratio***

	OR	95% CI bottom	95% CI top	p
Shorter FU				
Mean cortisol at night	1.271	0.940	1.719	0.11
Max. ACTH level after oCRH stimulation test (before TSS)	0.981	0.958	1.005	0.11
Longer FU				
Mean cortisol at night	1.163	0.957	1.413	0.10
Max. ACTH level after oCRH stimulation test (before TSS)	0.988	0.973	1.003	0.10

ACTH — adrenocorticotropic hormone; oCRH — ovine corticotropin-releasing hormone; TSS — transsphenoidal pituitary surgery; OR — odds ratio; CI — confidence interval

A unit increase of mean serum cortisol at night in odds ratio analysis increases the chance of recurrence by 16.3%. A unit increase of the value of max. serum ACTH after oCRH test reduces the chance of recurrence by 1.2% (p = 0.10) (Tab. 3).

In addition, ROC analysis was performed in both groups for the mean cortisol concentration at night and max. ACTH after oCRH test, and cut-off points for these variables were found. A significant threshold value (p < 0.001) of mean serum cortisol at night was found

and the best cut-off value for differentiating between remission and relapse was 17.5 μg/dL (sensitivity 70%, specificity 100%), and the receiver operating characteristic plot area under the curve (AUC) was 0.81. We found that an ACTH level of less than 98 pg/mL was the best cut-off value for differentiating between remission and relapse (sensitivity 63.2%, specificity 100%, p = 0.07, AUC = 0.70).

Discussion

Numerous researchers attempted to find the predictive factors of CD recurrence. However, the results are not conclusive and, currently, no universal predictive factor has been confirmed in all studies. The predictive factors reported in the literature regarding both the paediatric and adult populations are: younger age at the time of TSS, larger tumour diameter, no identification of adenoma in MRI/intraoperatively, dural/petrosal sinus invasion, early postoperative recovery of normal function of the hypothalamic-pituitary-adrenal axis, no histopathological confirmation of pituitary corticotroph adenoma, and, following recent publications, mutations in the *USP8* gene in the resected tumour tissue [5, 6, 8, 12, 18, 19].

In the presented study p was close to 0.05 for the following variables: the average cortisol level at night and max. ACTH level after oCRH test. This potentially signals a difference between the groups that, to be confirmed, requires further studies based on a larger sample. In the present study the increase of max. ACTH after oCRH reduced the likelihood of a recurrence (logistic regression ratio of –0.0123). In contrast, Lindsay et al. conducted a study in 332 patients (children and adults), which revealed that a higher level of ACTH values in oCRH test was a predictive factor for CD relapse [20]. In this study ACTH level was significantly lower in patients in a long-term remission compared to those who later experienced a recurrence (p < 0.007–0.02) [20].

A significantly elevated preoperative serum cortisol level was reported to be a predictive factor of CD recurrence in adults [21], while no study has confirmed this factor in children. Further studies should be conducted on larger samples to verify whether higher mean cortisol level at night could increase the possibility of recurrence after TSS.

In contrast to a study carried out by Devoe et al. [5], a positive correlation between younger age at the time of surgery and the recurrence was shown in our study (p = 0.55).

Moreover, our study did not confirm the previous results concerning CD predictive factors regarding the paediatric population [6, 8, 18]. Lonser et al. demonstrated that dural invasion or petrosal sinus invasion and no intraoperative identification of adenoma may constitute the prognostic factors of CD recurrence [6]. Lodish et al. [18] reported that an early recovery of hypothalamic-pituitary-adrenal axis after TSS may indicate a disease recurrence (in our study the time of HC substitution was a tested factor). Batista et al. associated the following factors with a relapse: the lack of histological confirmation of an adenoma, higher ACTH and cortisol responses to oCRH (oCRH test after TSS), and glucocorticoid replacement for less than six months postoperatively [8].

A limitation of our study is related to the fact that in many patients the recurrence status was not assessed biochemically at longer FU (in 75% of adult patients the data came from the questionnaire). Conversely, the extended FU is a major advantage of our study. The mean FU was 10.41 years, which is much longer than in other studies on the predictors of CD recurrence in children, e.g. Lonser et al. — 200 children with CD, mean postoperative follow-up 6.8 ± 4.7 yrs., range 0.3–21.3 [6]; Devoe et al. — 42 children, mean follow-up 7.2 yrs., range 1.5–13.6 [5]; Lodish et al. — 57 children, follow-up 6–36 months [18]; and Batista et al. — 72 children, follow-up 24–120 months [8]. Furthermore, the recurrence status could be confirmed on the basis of the questions in the questionnaire because they were very detailed. Moreover, a larger number of patients would be required to test the parameters mentioned above at the level of statistical significance of p < 0.05. Therefore, analysis with a shorter FU but based on the medical data from patient medical records with the biochemical assessment of the recurrence status was made. The average FU in this analysis is comparable with other studies conducted in the paediatric population. However, no prognostic factor was found in the group with shorter FU with the assumed statistical significance.

Conclusions

Cushing's disease recurrence may be diagnosed even a long time after effective treatment. It is possible that cortisol level at night and ACTH values in oCRH test before TSS may be helpful to predict which patients may experience a recurrence after successful initial treatment. However, further studies on a larger sample are needed to confirm this hypothesis.

Compliance with ethical standards

All authors declare that they have no conflict of interest. This article does not contain any studies with animals performed by any of the authors. All procedures performed in studies involving human participants were

in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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ORIGINAL PAPER

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