·颅底肿瘤·

库欣病患者术后即刻缓解影响因素分析

张文泰 王任直 冯铭

【摘要】 **目的** 筛查库欣病患者经鼻蝶入路手术后即刻缓解的影响因素。**方法** 纳入2014年1月至2020年8月在中国医学科学院北京协和医院行经鼻蝶入路手术的420例库欣病患者，单因素和多因素Logistic回归分析筛查术后即刻缓解的影响因素，绘制受试者工作特征曲线（ROC曲线）预测术后即刻缓解的截断值。**结果** 术后即刻缓解率为75.71%（318/420），Logistic回归分析显示，非首次手术（*OR* = 3.904，95%CI：2.199～6.930；*P* = 0.000）和术前高血浆促肾上腺皮质激素（ACTH）水平（*OR* = 0.995，95%CI：0.991～0.999；*P* = 0.027）是术后即刻缓解的危险因素。ROC曲线显示，术前血浆ACTH预测术后即刻缓解的曲线下面积为0.586（95%CI：0.524～0.648，*P* = 0.009），灵敏度为0.510，特异度为0.640，最佳阈值为85.45 pg/ml。**结论** 非首次手术和术前高血浆ACTH水平是库欣病患者经鼻蝶入路手术后即刻缓解的危险因素，内分泌科和神经外科医师在术前评估时应充分注意上述预后影响因素，并以此为依据做好医患沟通。

【关键词】 库欣综合征； 垂体肿瘤； 促肾上腺皮质激素； Logistic模型

Risk factors for immediate remission after operation in patients with Cushing´s disease

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【**Abstract**】 **Objective** To explore the preoperative factors affecting the immediate remission of Cushing′s disease after transsphenoidal surgery. **Methods** A total of 420 patients with Cushing′s disease (led by Dr. Feng Ming) in the Department of Neurosurgery of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College from January 2014 to August 2020 were included. Univariate and multivariate Logistic regression analyses were performed to find risk factors for immediate remission after operation of Cushing′s disease, and receiver operating characteristic curve (ROC) was used to predict the cut-off value of immediate remission after operation. **Results** Among 420 patients with Cushing′s disease, 318 patients had immediate remission after operation, and the immediate remission rate was 75.71%. Logistic regression analysis showed that non-primary surgery (*OR* = 3.904, 95%CI: 2.199–6.930; *P* = 0.000) and high adrenocorticotropic hormone level (*OR* = 0.995, 95%CI: 0.991–0.999; *P* = 0.027) were risk factors for immediate remission after opration in patients with Cushing′s disease. ROC showed the area under the curve (AUC), sensitivity and specificity of 85.45 pg/ml adrenocorticotropic hormone level (best threshold) for predicting immediate remission after operation were 0.586 (95%CI: 0.524–0.648, *P* = 0.009), 0.510 and 0.640. **Conclusions** Preoperative adrenocorticotropic hormone and the first operation are important factors affecting the immediate remission of patients with Cushing′s disease after transsphenoidal operation. Endocrinologists and neurosurgeons should pay attention to the factors affecting the prognosis of patients during the preoperative evaluation of patients with Cushing′s disease and make good communication between doctors and patients.

【**Key words**】 Cushing syndrome; Pituitary neoplasms; Adrenocorticotropic hormone; Logistic models

Conflicts of interest: none declared

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垂体促肾上腺皮质激素腺瘤亦称库欣病，循环血促肾上腺皮质激素（ACTH）水平升高[1]，皮质醇水平升高，从而导致一系列内分泌症状，如向心性肥胖、满月脸、乏力、体重增加、骨质疏松、糖尿病、皮肤菲薄等[2]。库欣病是库欣综合征最常见的病因，如果不能有效控制，病死率较高[3]。外科手术是首选治疗方法[4]，缓解率为52.1%～96.6%[5]、复发率为3%～66%[6-7]。既往有文献报道库欣病远期复发影响因素，主要为术后血清皮质醇、血浆ACTH和24小时尿游离皮质醇（24 hUFC）水平升高等[8-10]，性别、年龄、病程、症状严重程度和肿瘤对周围结构的侵袭等亦与肿瘤复发相关[11-12]；但也有学者认为，年龄、肿瘤大小和侵袭性与肿瘤复发无关联性[13]。上述研究结果并不完全一致，可能是样本量较小所致。Dai等[14]的队列研究显示，病程、首次手术、肿瘤大小、侵袭海绵窦、血浆ACTH水平是库欣病患者经鼻蝶入路手术后即刻缓解的影响因素，但该项研究并未将手术医师的经验纳入统计。本研究以中国医学科学院北京协和医院近年来诊断与治疗的420例库欣病患者为研究对象，基于样本量较大病例，避免既往研究局限性的同时，探究库欣病经鼻蝶入路手术后即刻缓解的相关影响因素。

资料与方法

一、临床资料

1.纳入标准 （1）经内分泌科、神经外科、放射科和病理科多学科诊疗共同诊断为库欣病。（2）存在高皮质醇血症临床症状。（3）头部MRI平扫和增强扫描提示垂体腺瘤，如果MRI增强扫描未发现肿瘤，则行动态对比增强MRI（DCE-MRI）验证。（4）符合内分泌诊断标准：清晨8∶00血清皮质醇水平＞615.20 nmol/L（110.36～615.20 nmol/L）或24 hUFC＞103.50 μg（12.30～103.50 μg）[15-16]。（5）所有患者均由同一位术者进行手术。

2.排除标准 （1）异位促肾上腺皮质激素综合征（EAS）患者。（2）未行经鼻蝶入路手术。（3）缺乏术后7 d内内分泌功能测定资料。

3.一般资料 选择2014年1月至2020年8月在北京协和医院神经外科行经鼻蝶入路手术的库欣病患者共420例，其中，男性80例，女性340例；年龄为5～73岁，平均（37.73±13.03）岁；体重指数（BMI）为12.82～52.35 kg/m^2，中位值为26.15（24.03，28.84）kg/m^2；病程为1～384个月，中位病程6（18，72）个月；首次手术者360例，非首次手术者60例；术前血清皮质醇水平为2.70～75.00 nmol/L，中位值为27.03（22.40，32.67）nmol/L；血浆ACTH水平为9.20～1060.00 pmol/L，中位值为73.00（50.55，105.00）pmol/L；24 hUFC 39.78～9969.12 μg，中位值432.38（271.16，723.56）μg；微腺瘤（最大径＜1 cm）379例，大腺瘤（最大径≥1 cm）41例。

二、研究方法

1.经鼻蝶入路手术 患者全身麻醉，仰卧位，头略向后仰，手术床头高脚底位。常规术野消毒铺巾，以络合碘消毒鼻腔及口唇，采用含去甲肾上腺素1 ml的棉片收缩中鼻甲黏膜5 min，于神经内镜（德国Karl Storz公司，0°镜头）下探查，行右侧鼻中隔带蒂黏膜瓣成形，高速磨钻磨开蝶窦腹侧壁，去除蝶窦内骨性纵隔及黏膜，消毒冲洗蝶窦腔；显微磨钻扩大鞍底骨窗至2 cm×2 cm，显微勾刀小心切开鞍底硬脑膜，沿鞍内肿瘤边界小心分离肿瘤，注意保护重要的垂体组织；肿瘤完全剥离后，以人工硬膜覆盖鞍膈，鞍内填塞凝胶海绵，带蒂黏膜瓣覆盖蝶窦后壁，蝶窦腔充填凝胶海绵，纳西棉填塞双侧鼻腔，并覆盖无菌辅料。

2.术后处理及术后即刻缓解 术后即刻予氢化可的松100 mg/次、2次/d静脉滴注，连续3 d后改为氢化可的松30 mg/d口服3 d；出院后每周序贯减量2.50 mg，直至氢化可的松维持剂量2.50～5.00 mg，停药需内分泌科和神经外科医师共同评估决定。术后3 d内每日清晨8∶00测量血清皮质醇水平，如果＜5 μg/dl（138 nmol/L）则予糖皮质激素替代治疗。“术后即刻缓解”定义为清晨8∶00血清皮质醇浓度＜5 μg/dl或者24 hUFC＜20 μg[17]。

3.统计分析方法 本研究有0.48%（2例）病程数据缺失、3.33%（14例）体重指数数据缺失、2.62%（11例）24 hUFC数据缺失、5.95%（25例）血清皮质醇数据缺失、3.10%（13例）血浆ACTH数据缺失，故在进行统计分析前，先采用K最近邻（KNN）算法行缺失值插补[18]。采用SPSS 23.0统计软件进行数据处理与分析，正态性检验采用Shapiro-Wilk检验。呈正态分布的计量资料以均数±标准差（$\bar{x}\pm s$）表示，采用两独立样本的t检验；呈非正态分布的计量资料以中位数和四分位数间距[$M(P_{25},P_{75})$]表示，采用Mann-Whitney U检验。计数资料以相对数构成比（%）或率（%）表示，采用χ^2检验。库欣病患者经鼻蝶入路手术后即刻缓解相关影响因素的筛查

表1 缓解组与未缓解组患者一般资料的比较

Table 1. Comparison of general data of Cushing's disease patients between remission group and non-remission group

观察指标	未缓解组（n=102）	缓解组（n=318）	统计量值	*P*值
性别[例(%)]			1.647	0.199
男性	15(14.71)	65(20.44)		
女性	87(85.29)	253(79.56)		
年龄($\bar{x}\pm s$,岁)	37.90±13.09	37.68±13.03	0.150	0.881
体重指数[$M(P_{25},P_{75})$,kg/m^2]	26.60 (24.30, 29.27)	25.99 (24.03, 28.46)	15 208.000	0.344
病程[$M(P_{25},P_{75})$,月]	42.00 (20.25, 84.00)	36.00 (18.00, 72.00)	15 074.000	0.283
首次手术[例(%)]	72(70.59)	288(90.57)	25.172	0.000
血清皮质醇[$M(P_{25},P_{75})$,nmol/L]	26.81 (23.03, 33.54)	27.28 (22.17, 32.33)	16 332.000	0.916
血浆ACTH[$M(P_{25},P_{75})$,pmol/L]	86.45 (55.40,112.75)	69.95 (46.35,104.00)	13 431.000	0.009
24 hUFC[$M(P_{25},P_{75})$,μg]	467.55 (290.16,839.95)	412.56 (270.23,679.33)	14 880.000	0.210
肿瘤直径[例(%)]			2.403	0.121
微腺瘤	88(86.27)	291(91.51)		
大腺瘤	14(13.73)	27(8.49)		

χ^2 test for comparison of sex, first operation and tumor diameter, two-independent-sample *t* test for comparison of age, and Mann-Whitney *U* test for comparison of others,性别、首次手术和肿瘤直径的比较行χ^2检验,年龄的比较行两独立样本的*t*检验,其余各项的比较行Mann-Whitney *U*检验。ACTH, adrenocorticotropic hormone,促肾上腺皮质激素;24 hUFC,24 h urinary free cortisol,24 h尿游离皮质醇

采用单因素和多因素前进法Logistic回归分析($\alpha_{入}=0.05$,$\alpha_{出}=0.05$)。绘制受试者工作特征曲线(ROC曲线)并计算曲线下面积(AUC),预测术后即刻缓解的截断值。以$P\leqslant0.05$为差异具有统计学意义。

结　果

本组420例患者术后即刻缓解318例(缓解组),术后未即刻缓解102例(未缓解组),两组一般资料比较,缓解组患者首次手术比例高于($P=0.000$)、血浆ACTH水平低于($P=0.009$)未缓解组,其余观察指标组间差异无统计学意义(均$P>0.05$,表1)。

单因素Logistic回归分析显示,首次手术($P=0.000$)和高血浆ACTH水平($P=0.014$)是术后即刻缓解的影响因素(表2,3)。将上述符合纳入与剔除标准的变量进一步纳入多因素Logistic回归方程,结果显示,非首次手术($OR=3.904$, 95%CI: 2.199~6.930; $P=0.000$)和高血浆ACTH水平($OR=0.995$, 95%CI: 0.991~0.999; $P=0.027$)是库欣病患者经鼻蝶入路手术后即刻缓解的危险因素(表4)。

ROC曲线显示,术前血浆ACTH预测术后即刻缓解的曲线下面积为0.586(95%CI: 0.524~0.648, $P=0.009$),灵敏度为0.510、特异度0.640,最佳阈值为85.45 pg/ml(18.80 pmol/L,图1),即术前血浆ACTH水平为85.45 pg/ml时,其预测术后即刻缓解的效能最大。

讨　论

本研究420例库欣病患者均行经鼻蝶入路手术,术后即刻缓解率为75.71%(318/420);进一步进行单因素和多因素Logistic回归分析,其结果显示,非首次手术和高血浆ACTH水平是术后即刻缓解的危险因素,而性别、年龄、体重指数、病程、血清皮质醇、24 hUFC和肿瘤直径并非术后即刻缓解的影响因素。

既往文献报道,库欣病患者经鼻蝶入路手术的缓解率为59.0%~96.6%[19],与本研究结果相一致。手术疗效是患者最为关注的问题,故探究术后即刻缓解相关影响因素对医患沟通较为重要。本研究结果显示,非首次手术是库欣病患者术后即刻缓解的危险因素,即非首次手术患者更易出现术后不缓解,与既往研究结果相一致[20]。目前对于非首次手术的库欣病患者的手术疗效研究较少,尚待进一步探究。本研究结果还显示,术前高血浆ACTH水平亦是库欣病患者术后即刻缓解的危险因素。Asuzu等[21]和Uvelius等[22]研究发现,术后内分泌激素如皮质醇、ACTH水平较高是库欣病患者预后不良的危险因素[21-22]。Dai等[14]认为,术前高ACTH水平是库欣病患者术后即刻缓解的危险因素,均与本研究结果相一致。进一步绘制ROC曲线,术前血浆ACTH预测术后即刻缓解的曲线下面积为0.586,灵敏度为0.510、特异度为0.640,截断值为85.45 pg/ml(18.80 pmol/L)。

既往对库欣病患者肿瘤直径是否影响预后尚存争议,Dai等[14]认为,大腺瘤是库欣病患者术后即刻缓解的危险因素($OR=0.575$, 95%CI: 0.405~0.817; $P=0.002$);而Starke等[23]的研究结果则与之相悖,微腺瘤患者术后即刻缓解率为96.67%(29/30),大腺瘤患者术后即刻缓解率为86.67%(13/15)。Blevins等[24]的研究显示,库欣病患者术前肿瘤直径较大可能导致术后肿瘤残留,从而影响术后即刻缓解率 。然而本研究结果显示,大腺瘤并非库

表2 库欣病患者术后即刻缓解相关影响因素的变量赋值表

Table 2. Variable assignment table of influencing factors for postoperative immediate remission after operation in patients with Cushing's disease

变量	赋值	
	0	1
术后即刻缓解	未缓解	缓解
性别	女性	男性
首次手术	否	是
肿瘤直径	微腺瘤	大腺瘤

表3 库欣病患者术后即刻缓解相关影响因素的单因素Logistic回归分析

Table 3. Univariate Logistic regression analysis of influencing factors for immediate remission after operation in patients with Cushing's disease

变量	*b*	*SE*	Wald χ^2	*P*值	*OR*值	*OR* 95%CI
男性	0.399	0.312	1.632	0.201	1.490	0.808～2.748
年龄	-0.001	0.009	0.023	0.880	0.999	0.982～1.016
体重指数	-0.037	0.026	2.067	0.150	0.963	0.915～1.014
病程	-0.002	0.002	0.570	0.450	0.998	0.994～1.003
首次手术	1.386	0.290	22.871	0.000	4.000	2.266～7.060
血清皮质醇	0.004	0.011	0.143	0.705	1.004	0.982～1.027
血浆ACTH	-0.005	0.002	6.088	0.014	0.995	0.991～0.999
24 hUFC	0.000	0.000	2.302	0.129	1.000	1.000～1.000
大腺瘤	-0.539	0.351	2.359	0.125	0.583	0.293～1.161

ACTH, adrenocorticotropic hormone, 促肾上腺皮质激素; 24 hUFC, 24 h urinary free cortisol, 24 h尿游离皮质醇

表4 库欣病患者术后即刻缓解相关影响因素的多因素前进法Logistic回归分析

Table 4. Multivariate forward Logistic regression analysis of influencing factors for immediate remission after operation in patients with Cushing's disease

变量	*b*	*SE*	Wald χ^2	*P*值	*OR*值	*OR* 95%CI
首次手术	1.362	0.293	21.633	0.000	3.904	2.199～6.930
血浆ACTH	-0.005	0.293	4.897	0.027	0.995	0.991～0.999
常数项	0.434	0.324	1.797	0.180		

ACTH, adrenocorticotropic hormone, 促肾上腺皮质激素

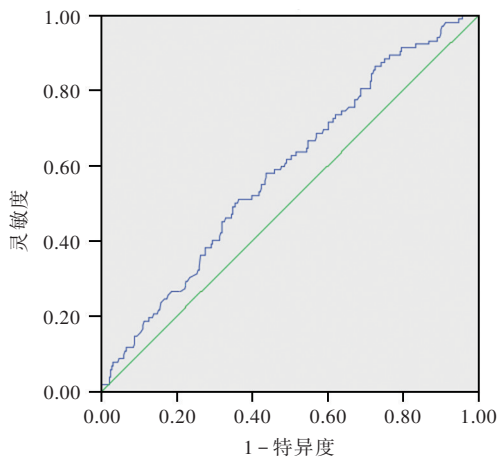

图1 ROC曲线显示,术前血浆ACTH预测术后即刻缓解的曲线下面积为0.586,灵敏度为0.510、特异度0.640,截断值为85.45 pg/ml

Figure 1 ROC showed the AUC, sensitivity and specificity of 85.45 pg/ml ACTH level (best threshold) for predicting immediate remission after operation were 0.586, 0.510 and 0.640.

欣病患者术后即刻缓解的危险因素。因此笔者认为,肿瘤大小对库欣病患者术后即刻缓解的影响取决于术者经验,如果术者经验不够丰富,处理较大肿瘤时有肿瘤残留之可能,尤其是肿瘤与海绵窦距离较近时。本研究所有患者均由冯铭教授主刀,他对库欣病的外科治疗有丰富经验,由他主刀的库欣病手术例数已超过700例,避免因不同经验术者造成数据存在混杂因素和偏倚。病程对于库欣病患者术后即刻缓解的影响同样存有争议[14,24]。一般认为,病程较长的患者可能症状更复杂多样,同时肿瘤体积可能更大,故术者在处理肿瘤时可能遇到更多困难。但也有学者认为,病程并非库欣病患者术后即刻缓解的重要影响因素[24]。本研究结果显示,病程长并非库欣病患者术后即刻缓解的危险因素。

本研究的优势在于:(1)所纳入患者均为同一术者实施手术,保证患者资料的真实性,避免因术者经验不同造成的临床资料混杂。(2)样本量较大。劣势在于:(1)患者临床资料存在缺失值,尽管通过人工智能算法对其进行填补,但仍可能影响结果,希望在今后工作中尽量减少缺失值。(2)ROC曲线显示的敏感性和特异性均较低。下一步拟扩大样本量进一步深入分析。

结　论

手术治疗作为库欣病的一线治疗方法,安全、高效,但其术后缓解率在不同医疗中心有所不同。北京协和医院神经外科冯铭教授主刀的420例库欣病患者的术后即刻缓解率为75.71%(318/420)。

Logistic回归分析显示，非首次手术和术前高血浆ACTH水平是库欣病患者术后即刻缓解的危险因素。后续希望进一步扩大样本量进行大样本多中心研究。

利益冲突 无

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