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超声引导下射频消融治疗继发性甲状旁腺功能亢进患者 严重低钙血症危险因素分析*

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[摘要] **目的** 研究超声引导下射频消融(RFA)治疗继发性甲状旁腺功能亢进(SHPT)患者术后发生严重低钙血症(SH)的危险因素。**方法** 选取2019年5月至2023年3月在川北医学院附属南充市中心医院接受RFA治疗的41例SHPT患者作为研究对象。采用回顾性分析,收集患者基础信息、疾病信息、实验室及影像学检查等数据。根据患者RFA术后1d血清校正钙水平是否低于1.8 mmol/L,将患者分为SH组与非SH组,利用单因素、多因素logistic回归模型分析RFA术后发生SH的相关危险因素,绘制受试者工作特征(ROC)曲线检测相关危险因素的预测效能。**结果** SHPT患者41例,男19例,女22例,平均年龄(49.56±13.64)岁,RFA术后1d发生SH者22例(SH组)。单因素分析结果显示,两组患者术前碱性磷酸酶(ALP)、C反应蛋白(CRP)、甲状旁腺激素(PTH)、血钙水平比较差异有统计学意义($P<0.05$)。多因素logistic回归分析结果显示,ALP是SHPT患者术后发生SH的独立危险因素。采用ALP预测SHPT患者RFA术后发生SH的ROC曲线下面积(AUC)为0.895,最佳预测截断值为323.34 U/L。**结论** 关注患者术前ALP水平并合理纠正,有利于降低术后SH发生率。

[关键词] 继发性甲状旁腺功能亢进;射频消融;低钙血症;继发

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Analysis on risk factors of severe hypocalcemia in ultrasound-guided radiofrequency ablation treatment in patients with secondary hyperparathyroidism*

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[Abstract] **Objective** To investigate the risk factors of postoperative severe hypocalcemia (SH) occurrence in the patients with secondary hyperparathyroidism (SHPT) treated by ultrasound-guided radiofrequency ablation (RFA). **Methods** A total of 41 patients with SHPT receiving RFA treatment in the Affiliated Nanchong Central Hospital of North Sichuan Medical College from May 2019 to March 2023 were selected as the study subjects. The retrospective analysis was adopted to collect the data such as the basic information, disease information, laboratory and imagiological examination. The patients were divided into the SH group and non-SH group according to whether or not the corrected serum calcium level being lower than 1.8 mmol/L on 1 d after RFA. The univariate and multivariate logistic regression models were used to analyze the related risk factors of SH occurrence after RFA. The receiver operating characteristic (ROC) curve was drawn to test the predictive efficiency of the related risk factors. **Results** There were 41 patients with SHPT, including 19 males and 22 females, with an average age of (49.56±13.64) years old, and 22 cases developed SH on 1 d after RFA. The univariate analysis results showed that preoperative alkaline phosphatase (ALP), C-reactive protein (CRP), parathyroid hormone (PTH), and serum calcium level comparison differences had statistical significance ($P<0.05$). Multivariate logistic regression analysis results showed that ALP was an independent risk factor for SH occurrence after RFA. The ROC curve area (AUC) of ALP predicting SHPT patients RFA postoperative SH was 0.895, and the best prediction cut-off value was 323.34 U/L. **Conclusion** Paying attention to the ALP level of patients before surgery and reasonable correction is beneficial to reduce the incidence of SH after surgery.

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tive protein (CRP), parathyroid hormone (PTH) and serum calcium levels had statistical differences between the two groups. The multivariate logistic regression analysis results showed that ALP was an independent risk factor for postoperative SH occurrence. The area under the curve (AUC) of adopting ALP for predicting SH occurrence after RFA in the patients with SHPT was 0.895, and the best predicted cut-off value was 323.34 U/L. **Conclusion** Paying attention to the level of ALP before operation and correcting it reasonably could be conducive to reduce the incidence rate of postoperative SH.

[Key words] secondary hyperparathyroidism; radiofrequency ablation; hypocalcemia; secondary

继发性甲状旁腺功能亢进 (secondary hyperparathyroidism, SHPT) 是慢性肾脏病 (chronic kidney disease, CKD) 患者常见的并发症, 约 26.3% 的 CKD 患者合并 SHPT^[1]。SHPT 主要表现为甲状旁腺增生, 甲状旁腺激素 (parathyroid hormone, PTH) 分泌过多, 并出现骨畸形、骨关节痛、瘙痒、异位钙化、心血管钙化等并发症, 会明显降低 CKD 患者的生活质量, 影响患者预后^[2-3]。SHPT 患者需要通过限制进食高磷食品, 加强透析, 服用磷酸盐结合剂、骨化三醇或维生素 D 类似物、拟钙剂等药物进行积极控制^[2], 但三发甲状旁腺功能亢进 (tertiary hyperparathyroidism, THPT) 患者及难治性 SHPT 患者, 药物治疗效果欠佳^[4]。目前改善全球肾脏病预后组织 (kidney disease: improving global outcomes, KDIGO) 指南建议对药物治疗无效的严重 SHPT 患者行甲状旁腺切除术 (parathyroidectomy, PTX)^[5]。

PTX 手术有一定风险, 创伤大, 切口愈合慢, 并发症较多, 且有严重心肺功能障碍的患者无法耐受手术。同时, 由于瘢痕、粘连和组织破坏, 患者可能在病情复发后不适合再次手术, 也有部分患者拒绝手术治疗^[6]。随着微创手术逐渐引入外科和医疗的各个领域, 有严重心肺功能障碍的透析患者可以选择创伤小、操作简单、重复性好的射频消融 (radiofrequency ablation, RFA)^[7-8]。低钙血症是 SHPT 手术患者的常见并发症, 发生率可达 75%~90%^[9]。严重低钙血症 (severe hypocalcemia, SH) 一直是常规手术及 RFA 术后临床及患者特别关注的问题, 会导致神经肌肉过敏、癫痫发作、心肌功能障碍和肺部异常等临床问题^[10], 甚至增高患者死亡风险^[11]。因此, 识别发生 SH 的危险因素, 早期积极干预十分关键。

1 资料与方法

1.1 一般资料

选取 2019 年 5 月至 2023 年 3 月在川北医学院附属南充市中心医院接受 RFA 治疗的 41 例 SHPT 患者作为研究对象。纳入标准: (1) 符合病史超过 3 个月, 且为 CKD 5 期的维持性血液透析患者; (2) 术前通过 B 超及核素显像检查证实有甲状旁腺增生, 显示至少 1 枚甲状旁腺增大, 且有丰富的血流信号; (3) 术前 PTH>800 pg/mL; (4) 药物治疗无效; (5) RFA 术

后第 1 天 PTH<300 pg/mL; (6) 病例资料完整。排除标准: (1) 活动性出血者; (2) 严重感染者; (3) 有恶性肿瘤者; (4) ECT 证实颈部以外存在异位的甲状旁腺疾病者。该研究经川北医学院附属南充市中心医院伦理委员会批准 [审批号: 2023 年审 (036) 号]。

1.2 方法

1.2.1 资料收集

性别, 年龄, 结节最大径, 基础疾病 (糖尿病、高血压), 术前实验室检查指标 [(PTH、碱性磷酸酶 (alkaline phosphatase, ALP)、C 反应蛋白 (C-reactive protein, CRP)、Hb、血清白蛋白、PLT、氨基末端脑钠肽前体 (N-Terminal pro-brain natriuretic peptide, NT-proBNP)、尿酸、血肌酐、血钙、血磷), B 超, 核素显像对甲状旁腺的检查。

1.2.2 SH 诊断标准和分组方法

依据肾脏病预后质量 (kidney disease outcomes quality initiative, KDOQI) 指南^[12], SH 定义为血清校正钙水平 ≤ 1.8 mmol/L。本研究依据 SHPT 患者 RFA 术后 1 d 血钙水平的监测情况, 分为 SH 组 (血清校正钙水平 ≤ 1.8 mmol/L) 和非 SH 组 (血清校正钙水平 > 1.8 mmol/L)。

1.3 统计学处理

采用 SPSS26.0 软件进行数据统计学处理, 符合正态分布的计量资料以 $\bar{x} \pm s$ 表示, 组间比较采用 t 检验; 非正态分布的计量资料以 $M(Q_1, Q_3)$ 表示, 组间比较采用秩和检验。计数资料以例数或百分比表示, 组间比较采用 χ^2 检验。采用单因素、多因素 logistic 回归分析 RFA 术后发生 SH 的相关危险因素, 绘制受试者工作特征 (receiver operating characteristic, ROC) 曲线分析相关危险因素的预测效能。以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者一般资料比较

SHPT 患者 41 例, 男 19 例、女 22 例。RFA 术后 1 d 发生 SH 患者 22 例 (SH 组), 未发生 SH 患者 19 例 (非 SH 组)。单因素分析结果显示, 两组术前 ALP、CRP、PTH、血钙水平比较, 差异有统计学意义 ($P < 0.05$), 见表 1。

2.2 多因素 logistic 回归分析结果

以单因素分析中差异有统计学意义的项目纳入多因素 logistic 回归分析,自变量均为连续变量。结果显示,术前 ALP 水平是术后 SH 的独立危险因素,见表 2。采用 ROC 曲线预测术前 ALP 水平对 SHPT

患者 RFA 术后发生 SH 的预测效能,曲线下面积(area under curve, AUC)为 0.895,最佳预测截断值为 323.34 U/L,见图 1。

表 1 两组患者一般资料比较

项目	SH 患者(n=22)	非 SH 患者(n=19)	OR	95%CI	P
男[n(%)]	10(45.45)	9(47.37)	0.926	0.270~3.171	0.902
年龄($\bar{x}\pm s$,岁)	47.96±11.23	51.42±15.79	0.981	0.937~1.028	0.422
结节最大径[M(Q ₁ ,Q ₃),mm]	20.30(15.30,22.50)	16.80(12.80,22.80)	1.055	0.953~1.168	0.300
高血压[n(%)]	14(63.64)	11(57.89)	1.273	0.362~4.480	0.707
糖尿病[n(%)]	2(9.09)	2(10.53)	0.850	0.108~6.695	0.877
Hb($\bar{x}\pm s$,g/L)	93.50±19.89	98.90±18.96	0.986	0.955~1.018	0.385
血清白蛋白($\bar{x}\pm s$,g/L)	41.66±4.08	42.25±3.35	0.959	0.814~1.131	0.622
PLT($\bar{x}\pm s$,×10 ⁹ /L)	149.00±60.03	137.79±59.08	1.003	0.993~1.014	0.551
血钙[M(Q ₁ ,Q ₃),mmol/L]	2.19(2.12,2.40)	2.41(2.27,2.55)	0.040	0.002~0.822	0.037
血磷($\bar{x}\pm s$,mmol/L)	2.05±0.62	2.12±0.61	0.835	0.308~2.267	0.724
ALP[M(Q ₁ ,Q ₃),U/L]	182.7(146.3,201.6)	680.1(456.8,782.6)	1.008	1.003~1.012	<0.001
NT-proBNP[M(Q ₁ ,Q ₃),pg/L]	8386.00(1544.00,35000.00)	3866.00(1907.00,8174.00)	1.000	1.000~1.000	0.400
PTH[M(Q ₁ ,Q ₃),pg/L]	2416.00(1910.00,3030.00)	1573.00(942.90,2244.00)	1.001	1.000~1.002	0.011
肌酐($\bar{x}\pm s$,μmol/L)	820.56±263.45	857.83±290.24	1.000	0.997~1.002	0.668
CRP[M(Q ₁ ,Q ₃),mg/L]	16.71(9.36,37.60)	4.32(2.83,10.30)	1.151	1.035~1.280	0.010

表 2 多因素 logistic 回归分析结果

项目	B	SE	Wald	OR	95%CI	P
血钙	-2.263	2.494	0.824	0.104	0.001~13.791	0.364
ALP	0.005	0.003	3.880	1.005	1.001~1.010	0.022
PTH	0.001	0.001	3.849	1.001	0.999~1.002	0.283
CRP	0.088	0.052	2.826	1.092	0.985~1.210	0.095

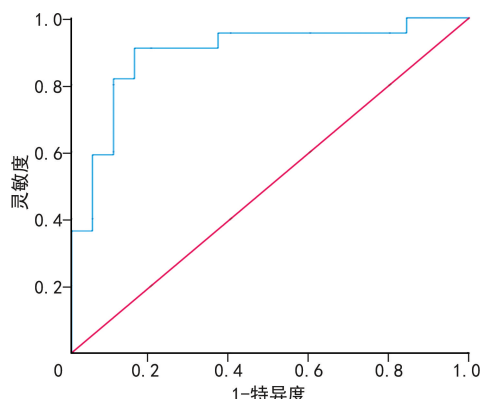


图 1 ALP 预测 RFA 术后发生 SH 风险 ROC 曲线

3 讨论

目前,针对 CKD 患者 SHPT 常见治疗方式包括药物治疗、PTX、RFA。相比于传统的 PTX,RFA 创伤小,操作简便,对患有严重心肺功能障碍的透析患者适应性更强,具有明显优势。同时,RFA 术后患者

骨痛、肌无力、食欲减退、失眠等症状可以得到明显改善,RFA 后血 PTH 达标率更高,较少出现声音嘶哑、活动性出血等并发症,疗效和安全性良好^[13]。但术后 SH 同样是困扰临床医生的难题,因此作者对 41 例经 RFA 术后的 SHPT 患者进行了回顾性研究。

结果显示,术前 ALP 水平是术后发生 SH 的独立危险因素,这与 HO 等^[14]、ZENG 等^[15]的研究结果一致。ALP 是一种公认的肾性骨营养不良生物标志物,也是 CKD 患者和普通人群致死率增加的生物标志物和危险因素。ALP 广泛分布于人体各脏器官中,主要由肝和成骨细胞分泌,反映了骨代谢的转运状态,ALP 水平越高,成骨细胞越活跃^[16]。PTH 水平在术后骤然下降,成骨-破骨细胞耦联活化异常,其动员破骨细胞的活性下降,骨钙释放入血减少,成骨细胞活性增加,血液中的钙离子大量转移至骨骼内参与成骨;ALP 水平越高,血钙下降越明显,更容易发生 SH。ZENG 等^[15]发现,相比于单次 RFA 治疗,分次 RFA 治疗的术后低钙血症发生率更低,ALP ≥ 566 mmol/L 的患者应分两次 RFA 治疗,以避免 SH 的发生,赵新萍等^[17]亦发现,将血钙水平 < 1.8 mmol/L 作为低钙标准时,ALP 低于截断值 566 mmol/L 的患者会出现 SH (灵敏度为 95.0%,特异度为 94.6%)^[17]。同时,还有研究发现,ALP 与早期的手术后低钙血症的发生呈正相关^[18]。本研究结果显示,

ALP>323.34 U/L 时,随着 ALP 升高,术后发生 SH 的风险递增。因此,术前关注 ALP 水平十分必要,对 ALP 水平过高的患者术前进行充分药物干预,抑制成骨细胞活跃,确定手术是否分次进行及做好 SH 的救治准备,可在一定程度上防止和降低患者术后发生 SH 的风险。

CKD 患者容易并发各种感染,感染是 CKD 患者的第 2 大死因,致死率高达 35%^[19]。微炎症状态是 CKD 的明显特征,维持性血液透析患者的微炎症状态发生率为 54%~75%^[20]。炎症状态下,肠内和肝脏 ALP 水平在机体启动炎症防御机制升高,炎症刺激和组织损伤可诱导机体产生三磷酸腺苷,ALP 可通过去磷酸化作用水解三磷酸腺苷,发挥抗炎和保护组织的作用;炎症细胞及凋亡坏死的组织细胞可释放 ALP,从而导致血清 ALP 水平升高^[21]。因此,术前可通过抗感染、纠正微炎症状态来降低术后发生 SH 的风险。另一方面,CKD 患者易合并心力衰竭^[22]。有研究报道,右心衰竭或右心充盈压升高可导致肝脏、肾脏淤血,而机体静脉淤血可引起血清 ALP 水平升高,提高 SH 发生率^[23]。同时,心力衰竭的患者可能更多使用利钠肽和加强超滤,也会引发机体电解质紊乱^[24]。因此,术前纠正心力衰竭、维持电解质平衡十分必要,可在一定程度上降低术后发生 SH 的风险。

既往有研究发现,血钙、PTH 水平也是术后发生 SH 的危险因素^[25-26],高水平的 PTH 会增加全因死亡风险^[27]。本研究单因素分析结果显示,两组患者血钙、PTH 水平比较差异有统计学意义($P<0.05$),但多因素分析结果中两者却并不是术后发生 SH 的独立危险因素,可能与纳入患者数量较少有关,后续可进一步纳入更多患者进行研究。

RFA 是 SHPT 患者良好的治疗手段,广泛应用于临床治疗中。RFA 术前 ALP 水平越高的患者术后更易出现 SH。了解 SHPT 患者 RFA 术后发生 SH 的危险因素,可为预防和治疗手术后低钙血症提供参考。但本研究为单中心回顾性研究,纳入患者例数偏少,可能对研究结论产生一定偏倚,需要在更大规模研究来对结论做进一步验证;由于缺乏长期随访数据,无法确定 RFA 治疗的长期疗效和安全性;其他未被考虑的因素(如患者的营养状况、并发症等)可能影响术后低钙血症发生情况。因此,未来的研究应该包括更大的样本量和延长随访期,以评估 RFA 的长期疗效和安全性。

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