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·临床研究·

血清COL1A1/2表达与颅内动脉瘤破裂的相关性研究

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[摘 要] **目的** 检测颅内动脉瘤(IA)患者血清Ⅰ型胶原蛋白α1链(COL1A1)、Ⅰ型胶原蛋白α2链(COL1A2)的表达水平,探讨其与动脉瘤破裂的相关性。**方法** 以我院收治的110例IA患者为IA组,另选取同期在我院进行健康体检的志愿者100例为对照组。采用ELISA法检测血清COL1A1、COL1A2表达水平。根据有无动脉瘤破裂将IA患者分为破裂组(n=66)与未破裂组(n=44),比较2组患者临床资料及血清COL1A1、COL1A2表达水平。比较不同Hunt-Hess分级患者血清COL1A1、COL1A2表达水平。采用多因素*Logistic*回归分析影响IA患者动脉瘤破裂的危险因素。采用受试者工作特征(*ROC*)曲线评估血清COL1A1、COL1A2对IA患者动脉瘤破裂的预测价值。采用*Spearman*相关性分析破裂组患者血清COL1A1、COL1A2与Hunt-Hess分级的相关性。**结果** IA组患者血清COL1A1、COL1A2表达水平均明显高于对照组(P<0.05)。破裂组患者高血压、糖尿病、高脂血症、动脉瘤直径>10 mm例数及COL1A1、COL1A2表达水平均明显多/高于未破裂组(P<0.05)。Hunt-Hess分级Ⅲ~Ⅳ级患者血清COL1A1、COL1A2表达水平明显高于Ⅰ~Ⅱ级患者(P<0.05)。破裂组患者血清COL1A1、COL1A2表达水平与Hunt-Hess分级均呈正相关(r=0.562、0.414,P<0.05)。多因素*Logistic*回归分析显示,高血压,糖尿病,动脉瘤直径>10 mm,COL1A1、COL1A2表达水平升高是IA患者动脉瘤破裂的危险因素(P<0.05)。血清COL1A1、COL1A2联合预测IA患者动脉瘤破裂的曲线下面积(*AUC*)显著大于COL1A1单独预测(Z=1.905,P=0.028)及COL1A2单独预测(Z=1.754,P=0.040)。**结论** COL1A1、COL1A2表达水平升高是IA患者动脉瘤破裂的危险因素,二者联合预测IA患者动脉瘤破裂有一定的临床价值。

[关键词] 颅内动脉瘤;Ⅰ型胶原蛋白α1链;Ⅰ型胶原蛋白α2链;动脉瘤破裂;相关性

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Correlation between expressions of serum COL1A1/2 and intracranial aneurysm rupture

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Abstract: Objective To detect the levels of serum collagen type Ⅰ alpha 1 chain (COL1A1) and collagen type Ⅰ alpha 2 chain (COL1A2) in patients with intracranial aneurysm (IA), and explore their correlations with aneurysm rupture. **Methods** A total of 110 IA patients admitted to our hospital were regarded as the IA group and another 100 volunteers who underwent physical examination in our hospital were regarded as the control group. The expression levels of serum COL1A1 and COL1A2 were detected by ELISA. The IA patients were divided into the ruptured group (n=66) and unruptured group (n=44) according to the presence or absence of aneurysm rupture, and the clinical data and expression levels of serum COL1A1 and COL1A2 were compared between the two groups. The expression levels of serum COL1A1 and COL1A2 in patients with different Hunt-Hess grades were compared. The risk factors of aneurysm rupture in patients with IA were analyzed by multivariate *Logistic* regression analysis. The predictive value of serum COL1A1 and COL1A2 for aneurysm rupture in patients with IA were evaluated by *receiver operating characteristic* (*ROC*) curve. The correlation of serum COL1A1 and COL1A2 with Hunt-Hess grade for patients in rupture group was analyzed by *Spearman* correlation analysis. **Results** The expression levels of serum COL1A1 and COL1A2 for patients in the IA group were significantly higher than those in the control group (P<0.05). The number of patients with hypertension, diabetes mellitus, hyperlipidemia, aneurysm diameter>10 mm, and the expression levels of serum COL1A1 and COL1A2 in the rupture group were significantly more/higher than those in the unruptured group (P<0.05). The expression levels of serum COL1A1 and COL1A2 in patients with Hunt-Hess grades from Ⅲ to Ⅳ were significantly higher than those in patients with grades from Ⅰ to Ⅱ (P<0.05). The expression levels of serum COL1A1 and COL1A2 for patients in the rupture group were positively correlated with Hunt-Hess grade (r=0.562, 0.414, P<0.05). Multivariate *Logistic* regression analysis showed that hypertension, diabetes mellitus, aneurysm diameter >10 mm, and increased expression levels of COL1A1 and COL1A2 were risk factors for aneurysm rupture in IA patients (P<0.05). The *area under the curve* (*AUC*) of aneurysm rupture predicted by serum COL1A1 and COL1A2 together was significantly higher than that predicted by COL1A1 alone (Z=1.905, P=0.028) and COL1A2 alone (Z=1.754, P=0.040). **Conclusion** The increased expression levels of serum COL1A1 and COL1A2 are risk factors for aneurysm rupture in patients with IA, and their combined prediction of aneurysm rupture in IA patients has certain clinical value.

Keywords: intracranial aneurysm; collagen type Ⅰ alpha 1 chain; collagen type Ⅰ alpha 2 chain; aneurysm rupture; correlation

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颅内动脉瘤(intracranial aneurysm,IA)是颅内局部血管壁受损后发生扩张膨出形成的瘤样突起,不属于肿瘤,我国该病发病率约为7%[1]。动脉瘤一旦发生破裂,则会诱发蛛网膜下腔出血,且预后较差[2];若治疗后再次发生破裂,则患者病死率更高[1]。由于IA初期症状不明显,患者在确诊时动脉瘤往往已经发生破裂,错过最佳的治疗时机。尽早发现对改善患者预后、挽救患者生命大有益处。随着分子技术的不断进步,越来越多的血液指标被发现是潜在的IA生物标志物[3]。Zhong等[4]通过对IA患者进行基因富集分析发现,Ⅰ型胶原蛋白α1链(collagen type Ⅰ alpha 1 chain,COL1A1)基因在IA患者中显著上调。另有研究发现,COL1A1与Ⅰ型胶原蛋白α2链(collagen type Ⅰ alpha 2 chain,COL1A2)受miRNA-513b-5p的调控,在IA患者中表达上调[5]。虽然COL1A1、COL1A2已被证实参与IA的发展,但两者是否可作为IA患者动脉瘤破裂的预测指标尚不明确。因此,本研究通过检测IA患者血清COL1A1、COL1A2的表达水平,探讨两者与动脉瘤破裂的相关性,旨在为该病的早期防治提供依据。

1 资料与方法

1.1 临床资料

将2020年1月至2021年6月我院收治的110例IA患者纳入IA组,另选取同时期在本院进行健康体检的志愿者100例为对照组。IA组患者中男61例,女49例;年龄35~74岁,平均(55.70±7.15)岁;平均BMI为(22.88±1.95)kg/m^2。对照组志愿者中男48例,女52例;年龄35~75岁,平均(54.95±7.31)岁;平均BMI为(22.46±1.89)kg/m^2。2组患者性别、年龄、BMI等资料比较,差异无统计学意义(P>0.05)。IA患者均行手术治疗,术后随访1年,根据患者有无动脉瘤破裂分为破裂组(经头部CT或腰椎穿刺证实)66例与未破裂组44例。破裂组患者根据Hunt-Hess分级[6]分为Ⅰ~Ⅱ级38例,Ⅲ~Ⅳ级28例。

纳入标准:IA患者经CT血管造影或数字减影血管造影检查确诊;首次确诊;临床资料完整。排除标准:合并其他脑部肿瘤或脑部疾病;颅脑手术史;有IA家族史;心、肝、肾等重要器官严重器质性病变。本研究经我院伦理委员会审批(20191103),所有研究对象或其直系亲属签署知情同意书。

1.2 方法

1.2.1 资料收集 患者入院后收集其基本资料,包括吸烟史、饮酒史、高血压、糖尿病、高脂血症、动脉瘤直径、动脉瘤个数、动脉瘤部位。

1.2.2 血清COL1A1、COL1A2表达水平检测 采集IA组患者入院次日清晨、对照组体检当日空腹静脉血5 mL,室温下静置30 min,置离心机中3 000 r/min离心15 min,分离出血清,然后置于-80 ℃冰箱保存待测。ELISA法检测血清COL1A1(批号:20180521)、COL1A2(批号:20190317)表达水平,严格按照试剂盒说明书进行操作,试剂盒均购自武汉菲恩生物科技有限公司。

1.3 统计学分析

使用SPSS 25.0软件进行统计学分析。计量资料经正态性检验符合正态分布,以均数±标准差($\bar{x}\pm s$)表示,行独立样本t检验;计数资料以频数表示,行χ^2检验。多因素*Logistic*回归分析IA患者动脉瘤破裂的影响因素;受试者工作特征(*receiver operating characteristic*,*ROC*)曲线评价血清COL1A1、COL1A2对IA患者动脉瘤破裂的预测价值,COL1A1、COL1A2单独预测与联合预测曲线下面积(*area under the curve,AUC*)的比较采用*Delong*检验;*Spearman*相关性分析破裂组患者血清COL1A1、COL1A2表达水平与Hunt-Hess分级的相关性。P<0.05为差异具有统计学意义。

2 结果

2.1 对照组与IA组患者血清COL1A1、COL1A2表达

IA组患者血清COL1A1、COL1A2表达水平均明显高于对照组(P<0.05),见表1。

表1 对照组与IA组患者血清COL1A1、COL1A2表达比较($\bar{x}\pm s$,ng/mL)

组别	n	COL1A1	COL1A2
IA组	110	10.01±3.06	7.69±2.48
对照组	100	3.04±0.95	2.59±0.82
t		21.837	19.609
P		0.000	0.000

2.2 破裂组与未破裂组患者临床资料及血清COL1A1、COL1A2表达比较

破裂组患者高血压、糖尿病、高脂血症、动脉瘤直径(>10 mm)患者例数及COL1A1、COL1A2表达水平均明显多/高于未破裂组(P<0.05),2组患者吸烟史、饮酒史、动脉瘤个数、动脉瘤部位比较差异无统计学意义(P>0.05),见表2。

2.3 IA患者动脉瘤破裂的多因素*Logistic*回归分析

以IA是否发生动脉瘤破裂(是=1,否=0)为因变量,以高血压(是=1,否=0)、糖尿病(是=1,否=0)、高脂血症(是=1,否=0)、动脉瘤直径(>10 mm=1,≤10 mm=0)、COL1A1(实测值)、COL1A2(实测值)表达水平为自变量进行多因素*Logistic*回归分析,结果显示,高血压,糖尿病,动脉瘤直径>10 mm,COL1A1、COL1A2水平较高是IA患者动脉瘤破裂的危险因素(P<0.05),见表3。

表2 破裂组与未破裂组患者临床资料及血清COL1A1、COL1A2表达比较

指标		破裂组（n=66）	未破裂组（n=44）	χ^2/t	P
吸烟史（例）		19	12	0.030	0.863
饮酒史（例）		16	10	0.034	0.855
高血压（例）		24	7	5.457	0.019
糖尿病（例）		25	7	6.177	0.013
高脂血症（例）		29	10	5.191	0.023
动脉瘤直径>10 mm（例）		12	2	4.420	0.036
动脉瘤个数（例）	1个	36	29	1.410	0.235
	≥2个	30	15		
动脉瘤部位（例）	颈内动脉	16	10	0.439	0.979
	前交通动脉	14	8		
	后交通动脉	9	7		
	大脑中动脉	14	11		
	其他	13	8		
COL1A1（ng/mL）		11.46±3.59	7.83±2.27	5.955	0.000
COL1A2（ng/mL）		8.76±2.90	6.08±1.86	5.427	0.000

表3 IA患者动脉瘤破裂的多因素*Logistic*回归分析

变量	B	SE	$Wald\chi^2$	OR	95%CI	P
高血压	0.701	0.241	8.463	2.016	1.257～3.233	0.036
糖尿病	1.148	0.526	4.761	3.151	1.124～8.835	0.029
高脂血症	0.181	0.126	2.056	1.198	0.936～1.534	0.152
动脉瘤直径	1.460	0.715	4.168	4.305	1.060～17.482	0.041
COL1A1	0.774	0.265	8.537	2.169	1.129～3.646	0.003
COL1A2	0.637	0.236	7.288	1.891	1.191～3.003	0.007

2.4 血清COL1A1、COL1A2对IA患者动脉瘤破裂的预测价值

*ROC*曲线结果显示，血清COL1A1单独预测IA患者动脉瘤破裂的*AUC*为0.791（95%*CI*: 0.706～0.877），敏感度、特异度分别为65.2%、88.6%，截断值为10.01 ng/mL；COL1A2单独预测IA患者动脉瘤破裂的*AUC*为0.799（95%*CI*:0.715～0.882），敏感度、特异度分别为66.7%、90.9%，截断值为7.82 ng/mL；两者联合预测的*AUC*为0.892（95%*CI*:0.831~0.952），敏感度、特异度分别为87.9%、77.3%，两者联合预测的效能显著大于COL1A1单独预测（Z=1.905，P=0.028）及COL1A2单独预测（Z=1.754，P=0.040），见图1。

2.5 不同Hunt-Hess分级患者血清COL1A1、COL1A2表达水平比较

Hunt-Hess分级Ⅲ～Ⅳ级患者血清COL1A1、COL1A2表达水平明显高于Ⅰ～Ⅱ级患者（P<0.05），见表4。

2.6 破裂组患者血清COL1A1、COL1A2表达水平与Hunt-Hess分级的相关性

*Spearman*相关性分析显示，破裂组患者血清COL1A1、COL1A2表达水平与Hunt-Hess分级均呈正相关（r=0.562、0.414，P<0.05）。

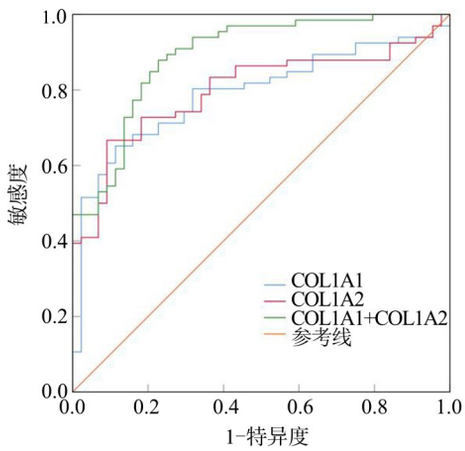


图1 血清COL1A1、COL1A2预测IA患者动脉瘤破裂的*ROC*曲线

表4 不同Hunt-Hess分级患者血清COL1A1、COL1A2表达水平比较（$\bar{x}\pm s$，ng/mL）

Hunt-Hess分级	n	COL1A1	COL1A2
Ⅰ～Ⅱ级	38	9.65±3.12	7.48±2.48
Ⅲ～Ⅳ级	28	13.92±4.23	10.50±3.46
t		4.723	4.133
P		0.000	0.000

3 讨论

IA是一种常见的脑血管疾病，其发病率呈逐年上升的趋势[7]。在动脉瘤未发生破裂时及时采取干预措施能够治愈；一旦动脉瘤发生破裂，其引起的蛛网膜下腔出血病死率高达50%[8]，经治疗后再次发生动脉瘤破裂的风险较高，且部分患者会出现长期的认知功能障碍[2]。尽早发现并评估IA患者动脉瘤破裂的风险有助于临床及时采取干预措施，改善患者预后。

COL1A1与COL1A2结合形成的Ⅰ型胶原蛋白是动脉壁的重要组成部分，胶原蛋白能够维持血管壁的弹性，并且具有抗牵拉的作用[9]。IA的形成主要是由于大脑动脉内部弹性层受到破坏，引起血管壁的重塑、细胞外基质成分和结构发生变化[10]。炎症、细胞外基质重建和平滑肌细胞耗竭在动脉瘤的形成和破裂中起着关键作用[11]。COL1A1已被证实能够诱导细胞外基质的合成和组织重塑[12-13]。Meng等[14]发现，COL1A2基因的单核苷酸多态性是IA的危险因素。本研究中IA患者血清COL1A1、COL1A2表达水平明显高于对照组，破裂组患者血清COL1A1、COL1A2表达水平明显高于未破裂组，与Zheng等[5]的研究结果一致。由于COL1A1、COL1A2表达上调，IA组织中Ⅰ型胶原蛋白大量形成，造成动脉瘤壁和细胞外基质持续性的胶原重塑，促进IA进展。同时，研究发现，miR-513b-5p/COL1A1/COL1A2能够通过调节RIP1-RIP3-MLKL和MMP通路促进血管平滑肌细胞坏死性

凋亡,诱导血管炎症反应,进而促进IA的进展[5]。本研究多因素*Logistic*回归分析发现,COL1A1、COL1A2水平较高是IA患者动脉瘤破裂的危险因素,推测COL1A1、COL1A2水平越高,动脉瘤壁和细胞外基质持续性的胶原重塑现象越严重,因而动脉瘤发生破裂的风险更高。此外,本研究中COL1A1、COL1A2联合预测IA患者动脉瘤破裂的敏感度及*AUC*更高,可为临床提供一定参考;破裂组患者血清COL1A1、COL1A2表达水平与Hunt-Hess分级均呈正相关,提示COL1A1、COL1A2表达水平与动脉瘤破裂出血的程度可能存在联系,但需后续进一步研究。

本研究中破裂组患者高血压、糖尿病、高脂血症、动脉瘤直径>10 mm患者例数均明显多于未破裂组,多因素*Logistic*回归分析显示,高血压、糖尿病、动脉瘤直径>10 mm是IA患者动脉瘤破裂的危险因素,与许刚柱等[15]的研究结果不完全一致,这可能是患者的个体差异及样本量较小导致。高血压会造成脑部动脉血管缺血缺氧或变性,从而发展为IA。糖尿病患者血糖较高,机体自由基生成增加而清除自由基系统受损,自由基氧化损伤蛋白质、脂质核酸等生物大分子,从而使动脉血管壁受损,发生IA的风险增高。同时,动脉瘤直径越大,其所承受的压力越大,破裂风险更高[16]。随着研究的不断深入,Toll样受体4[17]、中性粒细胞胞外诱捕网[18]、肥大细胞[19]等越来越多的因素被证明与IA患者动脉瘤破裂具有一定相关性。这说明影响IA患者动脉瘤破裂的因素较多,需要不断进行研究。

综上,IA患者血清COL1A1、COL1A2表达水平较高,是IA患者动脉瘤破裂的危险因素;两者联合预测IA患者动脉瘤破裂的敏感度较高,临床可根据IA患者血清COL1A1、COL1A2表达,并结合其他临床指标,准确预测脉瘤破裂,以便及时采取相应的干预措施。但本研究并未对不同Hunt-Hess分级的患者进行深入研究,这是本研究的不足之处。后续将扩大样本量,对COL1A1、COL1A2与动脉瘤破裂后蛛网膜下腔出血的严重程度进行研究,以期为临床提供参考。

[参考文献]

[1] 王雪文. 外科护理学[M]. 第9版. 北京:中国中医药出版,2012:6-8.

[2] 中国医师协会神经介入专业委员会,中国颅内动脉瘤计划研究组. 中国颅内破裂动脉瘤诊疗指南2021[J]. 中国脑血管病杂志,2021,18(8):546-574. doi:10.3969/j.issn.1672-5921.2021.08.007.

[3] 杨亚莲,张 赛,涂 悦,等. 血液中提示颅内动脉瘤形成的潜在标志物研究进展[J]. 中国医药,2020,15(7):1136-1139. doi:10.3760/j.issn.1673-4777.2020.07.039.

[4] Zhong A,Ding N,Zhou Y,et al. Identification of hub genes associated with the pathogenesis of intracranial aneurysm via integrated bioinformatics analysis [J]. Int J Gen Med, 2021, 14: 4039-4050. doi: 10.2147/IJGM.S320396.

[5] Zheng Z,Chen Y,Wang Y,et al. MicroRNA-513b-5p targets COL1A1 and COL1A2 associated with the formation and rupture of intracranial aneurysm[J]. Sci Rep,2021,11(1):14897. doi:10.1038/s41598-021-94116-5.

[6] Hunt WE,Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms[J]. J Neurosurg,1968,28(1):14-20. doi:10.3171/jns.1968.28.1.0014.

[7] Lee SU,Kim T,Kwon OK,et al. Trends in the incidence and treatment of cerebrovascular diseases in Korea:part Ⅰ. Intracranial aneurysm,intracerebral hemorrhage,and arteriovenous malformation[J]. J Korean Neurosurg Soc,2020,63(1):56-68. doi:10.3340/jkns.2018.0179.

[8] Schatlo B,Fung C,Stienen MN,et al. Incidence and outcome of aneurysmal subarachnoid hemorrhage:the Swiss study on subarachnoid hemorrhage (Swiss SOS)[J]. Stroke,2021,52(1):344-347. doi:10.1161/STROKEAHA.120.029538.

[9] 陈 艳,郑 峥,程 琼,等. 颅内动脉瘤患者血清hsa-miR-513b-5p水平及作用机制研究[J]. 中国实用神经疾病杂志,2021,24(12):1026-1034. doi:10.12083/SYSJ.2021.11.035.

[10] Texakalidis P,Sweid A,Mouchtouris N,et al. Aneurysm formation,growth,and rupture:the biology and physics of cerebral aneurysms[J]. World Neurosurg,2019,130:277-284. doi:10.1016/j.wneu.2019.07.093.

[11] Zhou T,Wang Q,Phan N,et al. Identification of a novel class of RIP1/RIP3 dual inhibitors that impede cell death and inflammation in mouse abdominal aortic aneurysm models[J]. Cell Death Dis,2019,10(3):226. doi:10.1038/s41419-019-1468-6.

[12] Tao R,Fan XX,Yu HJ,et al. MicroRNA-29b-3p prevents Schistosoma japonicum-induced liver fibrosis by targeting COL1A1 and COL3A1 [J]. J Cell Biochem,2018,119(4):3199-3209. doi:10.1002/jcb.26475.

[13] Gong N,Shi L,Bing X,et al. S100A4/TCF complex transcription regulation drives epithelial-mesenchymal transition in chronic sinusitis through Wnt/GSK-3β/β-catenin signaling[J]. Front Immunol,2022,13:835888. doi:10.3389/fimmu.2022.835888.

[14] Meng Q,Hao Q,Zhao C. The association between collagen gene polymorphisms and intracranial aneurysms:a meta-analysis [J]. Neurosurg Rev,2019,42(2):243-253. doi:10.1007/s10143-017-0925-x.

[15] 许刚柱,丁志斌,吴 涛. 血浆外泌体miR-145-5p在颅内动脉瘤患者中表达及与颅内动脉瘤破裂关系研究[J]. 创伤与急危重病医学,2021,9(2):135-137. doi:10.16048/j.issn.2095-5561.2021.02.13.

[16] 李不言,袁 盾,姜维喜,等. 颅内动脉瘤破裂的影响因素分析[J]. 国际神经病学神经外科学杂志,2019,46(3):246-250. doi:10.16636/j.cnki.jinn.2019.03.003.

[17] Mitsui K,Ikedo T,Kamio Y,et al. TLR4 (Toll-like receptor 4) mediates the development of intracranial aneurysm rupture [J]. Hypertension, 2020, 75 (2): 468-476. doi: 10.1161/HYPERTENSIONAHA.118.12595.

[18] Korai M,Purcell J,Kamio Y,et al. Neutrophil extracellular traps promote the development of intracranial aneurysm rupture [J]. Hypertension, 2021, 77 (6): 2084-2093. doi: 10.1161/HYPERTENSIONAHA.120.16252.

[19] Furukawa H,Wada K,Tada Y,et al. Mast cell promotes the development of intracranial aneurysm rupture[J]. Stroke,2020,51(11):3332-3339. doi:10.1161/STROKEAHA.120.030834.

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