血管性血友病因子裂解酶在脓毒性休克患者中低表达且对其预后有评估价值

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摘要 目的:探讨血管性血友病因子裂解酶(ADAMTS13)在脓毒性休克患者中的表达意义。方法:选取脓毒症患者 150 例,按严重程度分为单纯脓毒症组(43 例)、重度脓毒症组(48 例)、脓毒性休克组(59 例)。另外选取同期体检的健康志愿者 60 例作为健康对照组。检测脓毒症组患者确诊后第 1、3、5、7 天及健康对照组血浆 ADAMTS13 水平,并行急性生理与慢性健康状况评估(APACHEⅡ)评分,随访患者 28 d 预后情况,分析上述指标对患者预后的预测价值。结果:脓毒症组不同时间点血浆 ADAMTS13 水平均低于健康对照组(P 均 <0.05)。脓毒症 3 个亚组 ADAMTS13、血管性血友病因子(vWF)、抗凝血酶(AT)、白细胞介素(IL)-6 水平、APACHEⅡ评分比较,差异有统计学意义(P 均 <0.05)。单纯脓毒症组 ADAMTS13、AT 高于重度脓毒症组和脓毒性休克组且重度脓毒症组高于脓毒性休克组(P 均 <0.05),vWF、IL-6 水平、APACHEⅡ评分低于重度脓毒症组和脓毒性休克组,且重度脓毒症组低于脓毒性休克组(P 均 <0.05)。单纯脓毒症组和重度脓毒症组患者均无死亡病例。脓毒性休克组中存活 29 例,死亡 30 例,死亡率为 50.85%。脓毒性休克死亡患者血浆 ADAMTS13、AT 水平低于存活者,vWF、IL-6 水平、APACHEⅡ评分高于存活者(P 均 <0.05)。血浆 ADAMTS13、vWF、AT、IL-6 水平、APACHEⅡ评分为脓毒性休克患者预后的危险因素(P 均 <0.05)。ADAMTS13、vWF、AT、IL-6 水平、APACHEⅡ评分对脓毒性休克患者预后死亡的预测价值较高,其中以 ADAMTS13 预测价值最高(P 均 <0.05)。结论:脓毒性休克患者血浆 ADAMTS13 水平明显降低,降低程度与患者疾病严重程度及预后有关,可能与调控 vWF、AT、IL-6 水平表达,介导炎症、凝血障碍的发生相关。

关键词 血管性血友病因子裂解酶;血管性血友病因子;脓毒性休克;预后

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Low expression of ADAMTS13 in patients with septic shock and its prognostic value

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Abstract Objective: To explore the value of the ADAMTS13 expression in septic shock patients. Methods: 150 patients with sepsis were divided into 3 groups: mild sepsis group (43 cases), severe sepsis group (48 cases) and septic shock group (59 cases). A total of 60 healthy volunteers were selected as the control group. The ADAMTS13 activity in the peripheral blood of d1, d3, d5, d7 of sepsis patients enrolled into hospital and control group during physical examination were tested. The acute physiology and chronic health evaluation Ⅱ (APACHEⅡ) score was also recorded and compared within 4 groups. All patients were followed up for 28 days. Results: The ADAMTS13 activity [d1 (65.02 ± 2.16)%, d3 (59.65 ± 2.00)%, d5 (53.21 ± 1.02)%, d7 (50.12 ± 1.00)%] of all patients at different time points was lower than that of the control group [(80.49 ± 5.45)%] (all $P<0.05$). There were statistically significant differences in ADAMTS13 activity among 3 groups of sepsis at different time points (all $P<0.05$). The ADAMTS13 activity in the mild sepsis group was lower than the severe sepsis group and septic shock group (all $P<0.05$), and that in the severe sepsis group was lower than in the septic shock group ($P<0.05$). There were statistically significant differences in the ADAMTS13, von Willebrand factor (vWF), antithrombin (AT), interleukin-6 (IL-6) and APACHEⅡ scores among 3 groups of sepsis (all $P<0.05$). The ADAMTS13 and AT in the mild sepsis group were higher (all $P<0.05$), and the vWF, IL-6 and APACHEⅡ score were lower than those in the severe sepsis group and septic shock group (all $P<0.05$). The ADAMTS13 and AT in severe sepsis group were higher (all $P<0.05$), and vWF, IL-6 level and APACHEⅡ score were lower than in septic shock group (all $P<0.05$). There were no deaths in the mild sepsis group and severe sepsis group. In the septic shock group, 29 cases survived, 30 cases died, and the mortality rate was 50.85%. The ADAMTS13 activity and AT in patients who died from septic shock were lower than the survival patients in the septic shock group (all $P<0.05$). The vWF, IL-6 and APACHEⅡ score in patients who died from septic shock were higher than those in the survival patients in the septic shock group (all $P<0.05$). The ADAMTS13, vWF, AT, IL-6 and APACHE II scores were prognostic risk factors of patients with septic shock (all $P<0.05$). ADAMTS13, vWF, AT, IL-6 and APACHEⅡ scores had higher predictive value for the prognosis of death in patients with septic shock. Among them, ADAMTS13 had the highest predictive value (all $P<0.05$). Conclusion: Plasma ADAMTS13 in patients with septic shock is significantly reduced, which is related to the severity and prognosis. It may be related to the occurrence of inflammation and coagulopathy by regulating the expression of vWF, AT and IL-6.

Key words ADAMTS13; Von Willebrand factor; Septic shock; Prognosis

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脓毒性休克是指脓毒症导致低血压,经过临床液体治疗难以逆转,死亡率较高[1,2]。血管性血友病因子裂解酶(a disintegrin and metalloproteinase with thrombospondin type 1 motifs member 13,ADAMTS13)属于血管性血友病因子(von Willebrand Factor,vWF)的特异性裂解蛋白酶,经裂解血管性血友病因子结构 A2 区发挥生理作用,当其在机体内的活性降低时,会促使 vWF 聚集形成超大型血管性血友病因子多聚体,可导致血管内微血栓形成[3]。研究认为,ADAMTS13 可影响超大型血管性血友病因子多聚体识别裂解过程,在裂解 vWF 时不需借助血小板和血流剪切力[4]。脓毒性休克的发生与微血栓及凝血功能障碍相关,由此推测 ADAMTS13 可能参与了脓毒性休克的发生发展。本研究拟考察 ADAMTS13 在脓毒性休克患者中的表达,为脓毒性休克的诊治提供参考。

资料与方法

一般资料 选取 2017 年 1 月-2018 年 12 月新疆维吾尔自治区人民医院收治的脓毒症患者 150 例作为脓毒症组,根据患者疾病情况分为 3 个亚组:单纯脓毒症组、重度脓毒症组、脓毒性休克组。单纯脓毒症组 43 例(男 22,女 21),年龄 35 ~ 65,平均(45.3 ± 2.5)岁,原发疾病:创伤 22 例、肺部感染 16 例、腹部外科危重症 5 例;重度脓毒症组 48 例(男 23,女 25),年龄 35 ~ 68 岁,平均(46.1 ± 2.7)岁,原发疾病:创伤 25 例、肺部感染 14 例、腹部外科危重症 9 例;脓毒性休克组 59 例(男 27,女 32),年龄 35 ~ 66 岁,平均(45.9 ± 2.6)岁,原发疾病:创伤 15 例、肺部感染 8 例、腹部外科危重症 4 例。另外选取同期健康体检的健康志愿者 60 例(男 29,女 31),年龄 33 ~ 65 岁,平均(45.3 ± 2.6)岁。4 组研究对象性别、年龄等资料比较,差异无统计学意义(P 均 > 0.05),3 组脓毒症患者原发疾病等资料比较,差异无统计学意义(P > 0.05)。纳入标准:脓毒症诊断符合《2016 年脓毒症最新定义与诊断标准》。脓毒性休克符合《2014 国际严重脓毒症及脓毒性休克诊疗指南》的诊断标准[5]。排除标准:合并恶性肿瘤、自身免疫性疾病、急性心脑血管疾病、血液系统疾病、精神障碍者,感染性疾病患者。本研究经医院伦理委员会批准。患者及其家属均知情并签署同意书。

方法

1. ADAMTS13 活性检测。抽取脓毒症组确诊后第 1、3、5、7 天及健康对照组空腹外周静脉血 5 mL,放置于枸橼酸抗凝管中,以离心半径为 5 cm,转速 3 000 转/min 离心 10 min 后提取血浆,-80℃保存待用。使用双抗体夹心固相酶联免疫试剂盒检测 ADAMTS13 活性。

2. 急性生理与慢性健康状况评估(acute physiology and chronic health evaluation Ⅱ,APACHE Ⅱ)评分。对所有患者行 APACHE Ⅱ 评分,分数越高说明疾病越严重,预后越差。

3. 预后。对所有患者行 28 d 的随访,根据患者是否存活分为存活组和死亡组,比较 2 组患者血浆 ADAMTS13 活性、APACHE Ⅱ 评分。

4. 抗凝血酶(AT)、vWF、白细胞介素(IL)-6 水平检测。抽取脓毒症组患者确诊后第 1 天及健康对照组空腹外周静脉血 5 mL,采用法国 STA Analyzers 全自动凝血分析仪检测 AT 活性,采用酶联免疫吸附试剂盒检测 vWF、IL-6 水平。

统计学分析 采用 SPSS 20.0 统计学软件。计量资料采用($\bar{x} \pm s$)表示,多组间比较采用方差齐性检验,2 组间比较采用独立样本 t 检验,多因素采用 logistic 回归分析,使用 GraphPad Prism 软件绘制受试者工作特征曲线(receiver operating characteristic curve,ROC),使用 ROC 曲线下面积分析各指标对脓毒性休克患者预后的预测价值。以 $P < 0.05$ 为差异有统计学意义。

结 果

健康对照组和脓毒症组血浆 ADAMTS13 水平比较 脓毒症组不同时间点血浆 ADAMTS13 水平均低于健康对照组[d1(65.02 ± 2.16)%、d3(59.65 ± 2.00)%、d5(53.21 ± 1.02)%、d7(50.12 ± 1.00)% *vs* (80.49 ± 5.45)%,P 均 < 0.05]。

脓毒症患者血浆 ADAMTS13 水平比较 单纯脓毒症组不同时间点血浆 ADAMTS13 水平高于重度脓毒症组和脓毒性休克组(P 均 < 0.05),重度脓毒症组高于脓毒性休克组(P 均 < 0.05),见表 1。

脓毒症患者血浆 ADAMTS13、vWF、AT、IL-6 水平、APACHE Ⅱ 评分比较 单纯脓毒症组 ADAMTS13、AT 高于重度脓毒症组和脓毒性休克组,重度脓毒症组高于脓毒性休克组(P 均 < 0.05),单纯脓毒症组 vWF、IL-6 水平、APACHEⅡ评分低于重度脓毒症组和脓毒性休克组(P 均 < 0.05),重度脓毒症组低于脓毒性休克组(P 均 < 0.05),见表 2。单纯脓毒症组和重度脓毒症组患者均无死亡案例。脓毒性休克

组中存活29 例,死亡 30 例,死亡率为50.85%。脓毒性休克死亡患者血浆 ADAMTS13、AT 水平低于存活组(P 均 <0.05),vWF、IL-6 水平、APACHE Ⅱ 评分高于存活组(P 均 <0.05),见表 3。

影响脓毒性休克患者预后的危险因素分析 以脓毒性休克患者预后死亡为因变量,将血浆 ADAMTS13、vWF、AT、IL-6 水平、APACHE Ⅱ 评分为自变量纳入方程行多重线性回归,血浆 ADAMTS13、vWF、AT、IL-6 水平、APACHE Ⅱ 评分为影响脓毒性休克患者预后的危险因素(P 均 <0.05),见表 4。

各指标对脓毒性休克患者预后的预测价值 ADAMTS13、vWF、AT、IL-6 水平、APACHE Ⅱ 评分对脓毒性休克患者预后死亡的预测价值较高,其中以 ADAMTS13 预测价值最高 (P 均 <0.05),见表 5 和图 1。

讨 论

vWF 由内皮细胞合成,可与胶原纤维、血小板

表 1 脓毒症患者血浆 ADAMTS13 活性比较[$\bar{x} \pm s$,%]

组别	例	d1	d3	d5	d7
单纯脓毒症组	43	64.25 ± 2.15	60.25 ± 1.03*	59.69 ± 1.00$^{*\#}$	53.26 ± 1.00$^{*\#\triangle}$
重度脓毒症组	48	56.29 ± 1.62$^{\blacktriangle}$	52.13 ± 2.49$^{*\blacktriangle}$	49.68 ± 0.28$^{*\#\blacktriangle}$	45.67 ± 1.58$^{*\#\triangle\blacktriangle}$
脓毒性休克组	59	50.16 ± 3.49$^{\blacktriangle\square}$	48.25 ± 1.02$^{*\blacktriangle\square}$	43.25 ± 1.05$^{*\#\blacktriangle\square}$	38.79 ± 2.35$^{*\#\triangle\blacktriangle\square}$
F 值		35.124	87.648	119.485	56.870
P 值		0.001	0.001	0.001	0.001

注:与同组第 1d 比较,$^{*}P<0.05$;与同组第 3d 比较,$^{\#}P<0.05$;与同组第 5d 比较,$^{\triangle}P<0.05$;与单纯脓毒症组比较,$^{\blacktriangle}P<0.05$;与重度脓毒症组比较,$^{\square}P<0.05$

表 2 脓毒症患者血浆患者 ADAMTS13、vWF、AT、IL-6 水平、APACHE Ⅱ 评分比较($\bar{x} \pm s$)

组别	例	ADAMTS13(%)	vWF(%)	AT(%)	IL-6 水平(pg/mL)	APACHE Ⅱ 评分(分)
单纯脓毒症组	43	67.89 ± 5.67	1.34 ± 0.43	93.24 ± 5.32	19.56 ± 3.11	9.12 ± 2.34
重度脓毒症组	48	54.34 ± 3.54*	2.42 ± 0.78*	78.57 ± 9.34*	29.13 ± 3.49*	12.45 ± 3.01*
脓毒性休克组	59	41.08 ± 2.34$^{*\#}$	5.40 ± 0.91$^{*\#}$	67.00 ± 4.78$^{*\#}$	1201.29 ± 123.56$^{*\#}$	28.89 ± 3.23$^{*\#}$
F 值		586.402	402.819	190.408	4109.249	691.683
P 值		0.000	0.000	0.000	0.000	0.000

注:与单纯脓毒症组比较,$^{*}P<0.05$;与重度脓毒症组比较,$^{\#}P<0.05$

表 3 脓毒性休克存活组和死亡组患者 ADAMTS13、vWF、AT、IL-6 水平、APACHE Ⅱ 评分比较($\bar{x} \pm s$)

组别	例	ADAMTS13(%)	vWF(%)	AT(%)	IL-6 水平(pg/mL)	APACHE Ⅱ 评分(分)
存活组	29	68.79 ± 6.58	1.00 ± 0.05	84.25 ± 5.02	38.56 ± 3.65	10.58 ± 1.00
死亡组	30	14.29 ± 0.59	9.65 ± 1.03	50.32 ± 4.63	2325.26 ± 235.26	46.58 ± 5.12
t 值		445.190	40.810	27.000	52.320	37.170
P 值		0.001	0.001	0.001	0.001	0.001

表 4 影响脓毒性休克患者预后的危险因素分析

影响因素	β 值	SE	χ^2	P 值	OR(95% CI)
ADAMTS13 活性	1.125	0.536	8.254	0.000	1.857 ~ 8.574
vWF 活性	1.326	0.325	5.529	0.005	1.649 ~ 6.325
AT	1.168	0.657	3.247	0.012	1.528 ~ 4.329
IL-6 水平	1.147	0.542	4.263	0.009	1.326 ~ 5.247
APACHE Ⅱ 评分	1.329	0.865	2.354	0.016	1.025 ~ 3.587

表 5 各指标对脓毒性休克患者预后的预测价值

影响因素	曲线下面积(95% CI)	标准误	P 值	敏感度(%)	特异性(%)
ADAMTS13	0.800 ~ 0.964	0.832	0.001	86.39	70.12
vWF	0.765 ~ 0.812	0.800	0.025	80.23	72.63
AT	0.701 ~ 0.798	0.735	0.038	72.35	73.03
IL-6 水平	0.703 ~ 0.784	0.725	0.039	72.12	74.65
APACHE Ⅱ 评分	0.798 ~ 0.925	0.814	0.005	82.13	71.35

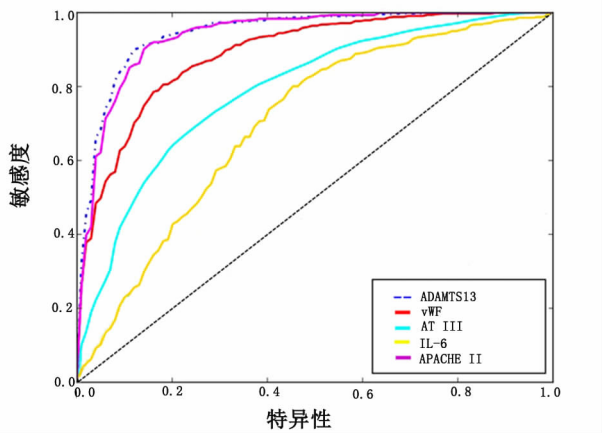

图 1 各指标预测脓毒性休克患者预后的 ROC 曲线

同时结合，当血管内皮损伤后，vWF会诱导血小板粘附于受损部位的胶原纤维，形成血栓促进凝血[6]。ADAMTS13 主要作用为剪切 vWF 多聚体来减少并抑制血栓形成，在肝脏可剪切 vWF 氨基酸 842-甲硫氨酸 843 间肽键，形成分子量不同的二肽和多肽[7,8]。机体在正常血流剪切力的作用下，血管内皮表面的 ADAMTS13 可在一定程度上介导 vWF 的剪切过程[9,10]。临床研究发现，脓毒症发生时，可促使 vWF 聚合物大量形成，过度消耗机体内 ADAMTS13[11]。脓毒症发生后机体处于严重炎症状态，机体内 IL-6 水平等炎症因子会过量表达，减缓 ADAMTS13 降解血管性血友病因子聚合物的速度。另外，脓毒症患者血浆 ADAMTS13 水平较健康人低，与 ADAMTS13 被过度消耗及 ADAMTS13 分泌异常有关[12,13]。当 ADAMTS13 在机体内含量不足且活性下降后，血浆中 vWF 聚合物不能被降解，在血流剪切力的作用下，同血小板膜表面的糖蛋白Ⅰb进行特异性的结合，形成大量血栓并阻塞微血管，加重机体微循环障碍，促进脓毒性休克发生，严重可致死亡[14]。本研究中脓毒性休克组中存活 29 例，死亡 30 例，死亡率为 50.85%。与存活患者比较，死亡患者的血浆 ADAMTS13 水平降低，APACHEⅡ评分升高，ADAMTS13 水平与脓毒性休克患者疾病严重程度明显相关，与衡军锋等[15]研究结果一致。

临床研究显示，在正常状态下血小板可沿着血管内皮细胞的流动不发生聚集、粘附作用，当血管壁被损伤后，血小板被激活并聚集粘附于血管壁上，进而导致微血栓形成和凝血的发生，此过程的发生与纤维蛋白原、vWF 等介导相关[16]。vWF 可同时与胶原纤维、血小板结合，当血管内皮发生损伤后，其可形成血栓，且具有稳定凝血因子Ⅷ的作用[17]。临床研究显示，在脓毒性休克发生后 AT 活性明显下降，患者凝血激活，血管内皮受损、毛细血管通透性增加等，与 vWF 协同作用[18]。另外，在脓毒性休克患者凝血障碍发生过程中炎症因子发挥着重要的作用，IL-6 水平在凝血启动过程中具有重要的意义[19]。ADAMTS-13 为 vWF 的特异性裂解蛋白酶，经裂解 vWF 因子结构上的 A2 区发挥其生理作用，当机体内的 ADAMTS-13 浓度或者活性降低后，vWF 会形成多聚体，导致血栓形成[20]。Martin 等[21]发现 ADAMTS13 在脓毒症患者血浆中活性显著降低，且与患者凝血功能障碍相关。本研究发现，ADAMTS13 可能通过介导 vWF、IL-6 水平、AT 表达加速疾病进展。ADAMTS13 活性降低与患者机体炎症-凝血障碍相关，本研究发现，血浆 ADAMTS13、vWF、AT、IL-6 水平、APACHEⅡ评分为脓毒性休克患者预后的危险因素（P 均 <0.05），ADAMTS13、vWF、AT、IL-6 水平、APACHEⅡ评分对脓毒性休克患者预后死亡的预测价值较高，其中以 ADAMTS13 预测价值最高（$P<0.05$）。

综上所述，脓毒性休克患者血浆 ADAMTS13 明显降低，且与患者疾病严重程度及预后有关，可能经调控 vWF、AT、IL-6 水平表达，介导炎症、凝血障碍的发生相关。

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