

老年急性脑出血并发癫痫患者血清 HP, SOD, MDA 水平表达及其与认知功能损害的相关性研究

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摘要: 目的 探讨老年急性脑出血并发癫痫患者血清触珠蛋白(haptoglobin,HP), 超氧化物歧化酶(superoxide dismutase,SOD), 丙二醛(malondialdehyde,MDA)的表达及其与认知损害的相关性。方法 选择2018年1月~2019年5月上海松江区中心医院神经内科住院的老年急性脑出血病人383例,按照是否发生癫痫,将患者分为癫痫发作组($n=123$)和癫痫未发作组($n=260$)。比较两组患者一般临床资料及血清HP, SOD和MDA水平;采用蒙特利尔认知评估量表(MoCA)对患者的认知功能进行评价。Spearman分析MoCA评分和血清HP, SOD和MDA水平的相关性。结果 与癫痫未发作组比较,癫痫发作组患者脑卒中史(25.20% vs 16.15%)、MoCA评分(22.76 ± 2.41 vs 24.38 ± 3.02),差异有统计学意义($\chi^2=4.432, P < 0.05; t=-5.214, P < 0.01$);发作组SOD(95.23 ± 12.13 u/ml vs 100.91 ± 12.95 u/ml)、HP(153.16 ± 27.00 mg/dl vs 166.06 ± 28.69 mg/dl)均低于未发作组,差异有统计学意义($t=-4.089, -6.741$, 均 $P < 0.01$),而发作组MDA高于未发作组(10.87 ± 3.32 nmol/ml vs 8.69 ± 2.48 nmol/ml),差异有统计学意义($t=7.174, P < 0.01$)。SOD与MoCA评分呈正相关($r=0.144, P=0.005$),HP与MoCA评分呈显著正相关($r=0.114, P=0.026$);而MDA与MoCA评分呈负相关($r=-0.145, P=0.004$)。结论 老年急性脑出血并发癫痫患者血清SOD,MDA,HP的表达水平与认知功能损害的严重程度相关,有助于评估患者的病情和预后。

关键词: 急性脑出血; 癫痫; 触珠蛋白; 血清超氧化物歧化酶; 丙二醛; 认知损害

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Study on the Correlation between Serum Haptoglobin, Superoxide Dismutase and Malondialdehyde in Elderly Patients with Epilepsy after Acute Cerebral Hemorrhage and Their Correlation with Cognitive Impairment

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Abstract: Objective To investigate the expression of serum haptoglobin (HP), superoxide dismutase (SOD), malondialdehyde (MDA) and their correlation with cognitive impairment in elderly patients with acute cerebral hemorrhage and epilepsy. **Methods** 383 elderly patients with acute cerebral hemorrhage from January 2018 to May 2019, in neurology department of Songjiang District Central Hospital in Shanghai were selected. According to whether epilepsy occurred, the patients were divided into epileptic attack group ($n=123$) and epileptic non attack group ($n=260$). The general clinical data, serum HP, SOD and MDA levels of the two groups were compared, and the cognitive function of the patients was evaluated by the Montreal Cognitive Assessment Scale (MoCA). Spearman analyzed the correlation between MoCA score and serum HP, SOD, MDA levels. **Results** Compared with the epileptic group, the stroke history (25.20% vs 16.15%, $\chi^2=4.432, P < 0.05$), MoCA score (22.76 ± 2.41 vs 24.38 ± 3.02 , $t=-5.214, P < 0.01$) and SOD (95.23 ± 12.13 u/ml vs 100.91 ± 12.95 u/ml), HP (153.16 ± 27.00 mg/dl vs 166.06 ± 28.69 mg/dl, $P < 0.01$) in the epileptic group were lower than those in the non epileptic group, the difference statistically significant ($t=-4.089, -6.741$, all $P < 0.01$), while MDA in the epileptic group was higher than that in the non epileptic group (10.8 ± 3.32 nmol/ml vs 8.69 ± 2.48 nmol/ml), the difference statistically significant ($t=7.174, P < 0.01$). SOD and MoCA scores was positively

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correlated ($r=0.144$, $P<0.05$). HP and MoCA scores was positively correlated ($r=0.114$, $P=0.026$), MDA and MoCA scores were negatively correlated ($r=-0.145$, $P=0.004$). **Conclusion** The expression of SOD, MDA, HP in serum of the elderly patients with acute cerebral hemorrhage complicated with epilepsy is related to the severity of cognitive impairment, which is helpful to evaluate the condition and prognosis of the patients.

Keywords: acute cerebral hemorrhage; epilepsy; haptoglobin, superoxide dismutase; malondialdehyde; cognitive impairment

脑出血发病凶险、病情恶化快,致死致残率高^[1],其并发症卒中后癫痫发作(post-stroke seizure, PSS)的发病率达到7%左右;65岁以上的老年新发癫痫患者,PSS比例高达30%~49%^[2]。癫痫和脑血管疾病存在共同的病理机制^[3]。有研究发现PSS患者,其认知损伤会随着癫痫的发展而加重进展^[4]。认知功能障碍是由癫痫因素和非癫痫因素等多种因素相互综合作用引起的常见并发症,主要包括神经递质异常、氧化应激失衡等^[5],而神经系统损伤继发的癫痫与氧化应激有关^[6]。急性脑出血血肿周围脑组织受到刺激产生的炎症因子可启动强大的氧化应激反应,进而加重脑组织的损伤。触珠蛋白(haptoglobin, Hp)是一种非常有效的抗氧化剂,通过与血红蛋白结合(hemoglobin, Hb)而减弱血浆中Hb的破坏作用,其表达量可在一定程度上提示神经系统病变的损伤程度。而自由基缓冲系统丙二醛(malondialdehyde, MDA)/血清超氧化物歧化酶(superoxide dismutase, SOD)在氧化应激反应中则具有重要的作用^[7]。

本研究选取老年急性脑出血患者,测定其血清HP、SOD和MDA水平,探究其与PSS的关系,并对HP、SOD和MDA的表达和认知损害相关性进行分析,为更深入地认识PSS提供参考依据。

1 材料与方法

1.1 研究对象 经上海市松江区中心医院伦理委员会批准,选择上海市松江区中心医院2018年1月~2019年5月神经内科收治住院的383例急性老年脑出血患者为研究对象。收集患者的临床资料:年龄、性别、吸烟史、饮酒史、高血压病史、糖尿病史、脑卒中史等;并记录体重指数(body mass index, BMI)、总胆固醇(total cholesterol, TC)、三酰甘油(triglyceride, TG)、低密度脂蛋白(low density lipoprotein, LDL)、高密度脂蛋白(high density lipoprotein, HDL)等。根据脑出血是否并发癫痫,分为癫痫发作组(123例)和癫痫未发作组(260例)。入选标准为:参考全国第四届脑血管病学术会议修订诊断要点,患者发病后24h内进行头颅CT检查,经2名高年资神经内科医师评定,诊断为急性脑出血;年龄65~75岁。排除标准为:①既往癫痫病史;②行急诊手术患者;③继发性脑出血(脑肿瘤、创伤性脑损伤、脑动静脉畸形、颅内动脉瘤、脑梗死后出血转化、脑出血

恢复期、脑出血后遗症);④排除服用抗凝药物、并发血液系统疾病、慢性肝肾功不全、恶性肿瘤及严重的心血管疾病等病人。⑤无影响神经心理检查的疾病(比如听力、视力严重障碍、失语等)。无精神病史:如抑郁、焦虑、精神分裂症等。所有患者均签署知情同意书。

1.2 试剂和仪器 体重计、身高尺。罗氏C8000全自动生化分析仪。HP试剂盒购自美国Ortho-Clinical Diagnostics, Inc。SOD和MDA检测试剂盒购自南京聚力生物医学工程研究所。严格按照试剂盒使用说明书进行操作。

1.3 方法

1.3.1 血清HP、SOD和MDA检测:采集2组患者的晨起空腹肘静脉血2ml,并以0.50ml枸橼酸钠溶液抗凝,静置30min,3000r/min离心10min,取上清液,于-80℃保存。采用ELISA法进行检测,以Bio-Rad酶标仪检测标准品及样本HP数值。采集2组患者的晨起空腹肘静脉血2ml,静置30min,3000r/min离心10min,取上清液,-20℃冰箱保存。采用黄嘌呤氧化酶法检测SOD活性,硫代巴比妥酸比色法检测MDA含量。血脂测定:TC, TG, LDL和HDL采用电化学发光法测定。

1.3.2 BMI测定:测量所有研究对象的身高、体重, $BMI(kg/m^2) = \text{体重} / \text{身高}^2$ 。

1.3.3 癫痫发作的定义:主要根据国际抗癫痫联盟的诊断标准:脑出血后癫痫发作指脑出血前无癫痫发作病史,在出现急性脑出血事件后一定时间内由于脑组织受损、并排除脑部其他及代谢性病变等导致的癫痫发作^[8]。

1.3.4 认知功能评价:采用蒙特利尔认知评估量表(MoCA)(北京版)^[9],包括执行控制/视空间功能、瞬时和5min延迟记忆、词语流畅性测试等共30分,测试结果正常值为>26分。如受教育年限≤12年则加1分。测试过程均采取统一的指导语,测试工具和测试环境,由经过培训的2名高年资神经内科医师操作。

1.4 统计学分析 采用SPSS24.0版软件对实验数据进行统计分析,计量资料以均数±标准差($\bar{x} \pm s$)表示,比较采用 t 检验;计数资料以率(%)表示,采用 χ^2 检验。采用Spearman相关分析对HP、SOD、MDA与MoCA评分进行相关分析。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组研究对象的一般资料比较 见表1。与未发作组相比,发作组患者年龄、性别、高血压、糖尿病、冠心病病史、吸烟、饮酒等基本资料比较,差异均无统计学意义(均 $P>0.05$)。而脑卒中史差异有统计学意义($P<0.05$)。

2.2 两组患者MoCA评分、BMI,血脂以及血清HP,SOD,MDA水平比较 见表2。与未发作组相比,发作组患者TC,TG,LDL,HDL和BMI等差异均无统计学意义(均 $P>0.05$)。MoCA评分以及HP,SOD,MDA水平差异均有统计学意义(均 $P<0.01$)。

表1 两组研究对象一般资料比较 [n(%)]

类别	发作组(n=123)	未发作组(n=260)	χ^2	P
年龄(岁)	69.21±6.40	67.92±6.07	1.908	0.057
男性	76(61.79)	165(63.46)	0.100	0.752
吸烟	41(33.33)	84(32.31)	0.040	0.842
饮酒	45(36.59)	92(35.38)	0.052	0.819
冠心病	34(27.64)	63(24.23)	0.514	0.473
高血压	91(73.98)	197(75.77)	0.143	0.706
糖尿病	49(39.84)	92(35.38)	0.712	0.399
脑卒中史	31(25.20)	42(16.15)	4.432	0.035

表2 两组研究对象MoCA评分、BMI,血脂以及血清HP,SOD,MDA检测水平比较 ($\bar{x}\pm s$)

项目	发作组(n=123)	未发作组(n=260)	t	P
TG (mmol/L)	1.85±0.73	1.81±0.59	0.573	0.567
TC (mmol/L)	3.59±1.23	3.42±0.97	1.465	0.144
HDL (mmol/L)	1.27±0.15	1.29±0.21	-0.948	0.344
LDL (mmol/L)	3.89±1.52	3.63±1.29	1.737	0.083
BMI (kg/m ²)	24.12±2.52	23.69±2.84	1.433	0.153
SOD(u/ml)	95.23±12.13	100.91±12.95	-4.089	0.000
MDA (nmol/ml)	10.87±3.32	8.69±2.48	7.174	0.000
HP(mg/dl)	153.16±27.00	166.06±28.69	-6.741	0.000
MoCA评分(分)	22.76±2.41	24.38±3.02	-5.214	0.000

2.3 血清中SOD,MDA,HP含量与认知功能损害的相关性分析 Spearman相关分析显示,MDA与MoCA评分呈显著负相关($r=-0.145$, $P=0.004$),SOD与MoCA评分呈显著正相关($t=0.144$, $P=0.005$),HP与MoCA评分呈显著正相关($r=-0.114$, $P=0.026$)。

3 讨论

脑卒中患者癫痫发病率高,有文献报告PSS随着年龄的增长而增加^[10],而且PSS会加重脑卒中患者病情^[11]。而认知功能障碍是老年癫痫患者最常见的并发症。既往有关PSS与认知功能之间的研究较少,因此,本研究拟评估老年急性脑出血并发癫痫

患者血清相关分子水平与氧化应激及认知障碍之间的相关性。反映氧化应激的最常用指标是SOD和MDA,其与癫痫的病理机制密切相关^[12]。SOD可清除生物体内自由基,SOD下降破坏了氧化-抗氧化平衡系统,诱导氧化损伤,进而参与癫痫的发作;而MDA是癫痫发作的异常代谢产物同时通过损伤脑神经促进癫痫发作,具有细胞毒性^[13-14],其含量间接反映了氧自由基含量和神经细胞损伤程度。HP是 $\alpha 2$ 球蛋白中的一种酸性糖蛋白,与出血性疾病关系密切,主要生理功能是参与游离Hb的代谢,通过与游离Hb结合形成HP-Hb复合物,避免游离Hb的氧化修饰^[15],从而抑制Hb诱导组织氧化损伤,所以Hp具有抗氧化的作用。本研究显示癫痫发作患者血清SOD,HP的表达下降($P<0.01$),而MDA表达则明显上升($P<0.01$),提示HP,SOD,MDA可能参与到脑出血并发癫痫的生物电活动中。进一步说明老年急性脑出血并发癫痫发病过程与氧化应激密切相关。

随年龄增长认知功能下降主要与中枢神经退行性变有关;而脑出血后癫痫发作是一种病理状态,癫痫发作会加重患者脑部缺氧并延长脑缺氧的时间,进而加重神经元损伤而引起认知障碍。本研究结果显示癫痫发作组患者认知功能损害重于未发作组($P<0.01$)。而且血清中SOD,MDA,HP水平与认知功能损害有关($P<0.05$),SOD,HP水平越高,患者MoCA评分越高,认知功能损害越轻($P<0.05$)。而MDA含量越高,患者认知功能损害越显著($P<0.01$)。表明血清SOD,MDA,HP水平可以在一定程度上反映老年急性脑出血并发癫痫患者认知功能损害的严重程度,对于评估患者病情及预后具有一定的参考价值。

综上所述,临床上可通过检测血清中SOD,MDA,HP水平来判断PSS的认知损害的严重程度和短期预后情况。可为PSS患者预后评估提供参考依据。但本研究收集患者血标本检测血清中SOD,MDA,HP均在患者入院次日,此时患者并未发生卒中相关性肺炎等并发症,不会影响血清SOD,MDA,HP水平与认知损害相关性的最终结果。本研究未进行后期随访,并且选择的患者资料具有单中心性特点,研究结果可能存在一定局限,有待多中心及大样本的前瞻性研究及基础实验对这一问题进行更深入的探索,为揭示HP,SOD,MDA在PSS中的作用提供进一步的理论依据。

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