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血清 CysC 及尿 NGAL 在百草枯中毒患者急性早期肾损伤中诊断价值

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摘要 目的:探讨血清半胱氨酸蛋白酶抑制剂 C(CysC)及尿性粒细胞明胶酶相关脂质运载蛋白(NGAL)在百草枯中毒患者急性早期肾损伤(AKI)中的诊断价值。**方法:**选择 2011 年 3 月至 2015 年 3 月我院收治的 300 例百草枯中毒患者为病例组,另选取来我院 150 例健康体检者为对照组,病例组根据是否发生 AKI 分为 AKI 组与非 AKI 组,各 150 例,采用酶联免疫吸附法检测 NGAL、肌氨酸氧化酶法检测血清肌酐(Scr)水平、免疫透射比浊法检测 CysC 水平,观察所有对象入院后 15 min、2 h、4 h、8 h、12 h、24 h、48 h、3 d、5 d、7 d Cys C、NGAL 以及 Scr 表达水平的变化。**结果:**AKI 组和非 AKI 组患者入院后 8 h、12 h、24 h、48 h、3 d、5 d、7 d 的 Scr 水平均高于对照组,差异具有统计学意义 ($P<0.05$);AKI 组患者入院后 12 h、24 h、48 h、3 d、5 d、7 d Scr 水平明显高于非 AKI 组,差异具有统计学意义($P<0.05$);AKI 组入院后 2 h、4 h、8 h、12 h、24 h、48 h、3 d、5 d、7 d,非 AKI 组入院后 8 h、12 h、24 h、48 h、3 d、5 d、7 d 的 NGAL 水平明显高于对照组,差异均有统计学意义($P<0.05$);AKI 组患者 NGAL 水平在入院后 48 h 升至峰值,而后开始缓慢下降,且 AKI 组入院后 4 h 的 NGAL 水平便开始明显高于非 AKI 组 ($P<0.05$);AKI 组基本在入院后 8 h、非 AKI 组在入院后 12 h 的 Cys C 水平便明显高于对照组($P<0.05$),AKI 组基本在入院后 3 d 升至峰值,而后开始缓慢下降,且 AKI 组在入院后 12 h 的 Cys C 水平便开始明显高于非 AKI 组,差异具有统计学意义($P<0.05$)。**结论:**血清 CysC 及尿 NGAL 水平在百草枯中毒后短时间内会出现异常升高,对早期诊断 AKI 具有积极意义。

关键词:CysC;NGAL;百草枯中毒;急性早期肾损伤

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Diagnostic Value of Serum CysC and Urinary NGAL of Acute Kidney Injury in Patients with Paraquat Poisoning

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ABSTRACT Objective: To investigate the diagnostic value of serum Cystatin C (CysC) and urinary neutrophil gelatinase associated lipocalin(NGAL) of acute kidney injury(AKI) in patients with paraquat poisoning. **Methods:** Selected 300 cases of patients with paraquat poisoning who treated in our hospital from March 2011 to March 2015 as the case group, and 150 cases of healthy physical examination subjects as the control group, case group was divided into AKI group and non AKI group according to whether occurrence of AKI, with 150 patients in each group, detected the NGAL by enzyme linked immunosorbent assay, and detected the serum creatinine (Scr) level by Muscle ammonia oxidase method, and detected CysC level by immune transmission turbidity method, observed the change of expression level of CysC, NGAL in all objects at 15 min, 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, 3 d, 5 d, 7 d after admission. **Results:** The Scr levels of AKI group and non AKI group were significantly higher than control group at 8 h, 12 h, 24 h, 48 h, 3 d, 5 d, 7 d after admission, the differences were statistically significant($P<0.05$); The Scr levels of AKI group were significantly higher than non AKI group at 12 h, 24 h, 48 h, 3 d, 5 d, 7 d after admission, the differences were statistically significant ($P<0.05$); The NGAL levels of AKI group at 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, 3 d, 5 d, 7 d after admission, and non AKI group at 8 h, 12 h, 24 h, 48 h, 3 d, 5 d, 7 d after admission were significantly higher than control group, the differences were statistically significant ($P<0.05$); The NGAL level in AKI group at 48h after admission to the peak, then decreased slowly, and the NGAL level of AKI group was began significantly higher than non AKI group at 4h after admission, the differences were statistically significant($P<0.05$); The CysC levels of AKI group at 8 h after admission, and non AKI group at 12 h after admission were began significantly higher than control group, the differences were statistically significant($P<0.05$), the CysC level of AKI group rose to the peak at 3 d after admission, and then began to slow down, and the CysC level in AKI group was began significantly higher than that in non AKI group at 12 h after admission, the differences were statistically significant($P<0.05$). **Conclusion:** The serum CysC and urinary NGAL levels in a short period after the paraquat poisoning will be unusually high, which has a positive significance for the early diagnosis of AKI.

Key words: Cystatin C; Neutrophil gelatinase-associated lipocalin; Paraquat poisoning; Acute kidney injury

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前言

百草枯中毒会造成机体多器官功能损害,目前尚缺乏特效的治疗方法,临床死亡率比较高^[1]。既往文献多关注的是百草枯中毒后肺损伤,但在临床实际中不难发现相当一部分的百草枯中毒早期死亡病例存在肾功能异常的现象,所以需要予以更多的重视^[2]。据报道,几乎 30%~50%的危重症患者有并发急性肾损伤(Acute kidney injury, AKI)的危险,其中 29%~90%会因该并发症而致死,这与缺乏有效的早期诊断指标有很大的关系^[3]。目前看来,血清肌酐(Serum creatinine, Scr)等临床用以反映 AKI 的常规指标由于不能及时与肾功能变化保持一致的步调,延迟性明显,所以需要更为积极地探究能够早期有效反映 AKI 的生物标志物^[4]。血清半胱氨酸蛋白酶抑制剂 C(Cystatin, CysC)与尿性粒细胞膜脂酶相关脂质运载蛋白(neutrophil gelatinase-associated lipocalin, NGAL)已在既往的报道中多次出现^[5],并被认为是具有早期诊断 AKI 的价值,本研究现将之用于百草枯中毒患者,以期对临床工作提供有益的参考。

1 资料与方法

1.1 一般资料

选择我院 2011 年 3 月至 2015 年 3 月期间收治百草枯中毒患者 300 例为病例组,纳入标准:①患者均经过确诊为百草枯中毒,并且了解药物来源,就诊时间为中毒 2h 内。②患者均经过紧急救治,无生命危险。③患者均为口服中毒。排除标准:①患者具有农药中毒史,或者后遗症等。②患者生命垂危,需要紧急手术或者抢救者。③合并其他药物中毒者。病例组男 183 例,女 117 例,年龄 19~57 岁,平均(34.28±5.26)岁,发病到就诊时间 0.2~2h,平均(1.14±0.25)h,病例组根据是否发生 AKI 分为 AKI 组与非 AKI 组,各 150 例,AKI 的诊断标准为 Scr≥(100.35±28.26)μmol/L^[6]。其中 AKI 组男 91 例,女 59 例;年龄 20~60 岁,平均年龄(33.89±4.15)岁;非 AKI 组男 89 例,女 61 例;年龄 21~59 岁,平均年龄(34.16±3.69)岁;另选取来我院 150 例健康体检者为对照组,其中男 89 例,女 61 例,年龄 22~54,平均为(32.45±4.89)岁;三组对象年龄、性别等基本资料间差异无统计学意义(P>0.05),具有可比性。

1.2 方法

对照组于体检当日、病例组于入院后 15 min、2 h、4 h、8 h、12 h、24 h、48 h、3 d、5 d、7 d 采集空腹静脉血 5 mL、尿液 5 mL,采集标本均以 3000 r/min 速度离心 5 min,留取血清和尿液上清液,储存于 -20℃ 待用。血清 Cys C 检测采用免疫投射比浊法,原理为样本中 Cys C 与偶联在胶乳颗粒上的抗胱抑素 C 抗体特异性结合,并引起凝集,凝集而引起的透射光减弱程度可被光学仪器检测,样本中胱抑素 C 浓度与透射光减弱成比例。使用多点定标,将病人样本获得的信号值(A)带入标准曲线,即可计算出胱抑素 C 的浓度(mg/L),人胱抑素 C 检测试剂盒购自上海荣盛生物药业有限公司。

NGAL 测定采用酶联免疫吸附法,人(NGAL)Elisa 试剂盒购自上海广锐生物科技有限公司;Scr 采用肌氨酸氧化酶法检测,血清肌酐购自北京博迈斯科技发展有限公司,严格按说明书进行操作。

1.3 研究指标

对照组、AKI 组、非 AKI 组在入院后 15 min、2 h、4 h、8 h、12 h、24 h、48 h、3 d、5 d、7 d Cys C、NGAL 以及 Scr 的水平变化。

1.4 统计学方法

采用 SPSS13.0 软件,计量资料以均值±标准差($\bar{x} \pm s$)表示,组间比较采取 t 检验,多组比较用方差分析。P<0.05 表示差异具有统计学意义。

2 结果

入院后 AKI 组和非 AKI 组 15 min、2 h、4 h Scr 水平与对照组间差异无统计学意义(P>0.05),入院后 AKI 组和非 AKI 组 8 h、12 h、24 h、48 h、3 d、5 d、7 d Scr 水平均高于对照组水平,差异具有统计学意义(P<0.05);入院后 12 h、24 h、48 h、3 d、5 d、7 d AKI 组 Scr 水平明显高于非 AKI 组,差异具有统计学意义(P<0.05)。病例组入院后 15 min 的 Cys C 及 NGAL 水平与对照组无明显差异(P>0.05),随着时间的推移 Cys C 及 NGAL 水平逐渐升高,AKI 组基本至入院后 2 h、非 AKI 组在入院后 8 h 的 NGAL 水平便明显高于对照组,差异具有统计学意义(P<0.05),AKI 组在入院后 48 h 升至峰值,而后开始缓慢下降,且 AKI 组入院后 4 h 的 NGAL 水平便开始明显高于非 AKI 组(P<0.05);AKI 组在入院后 8 h、12 h、24 h、48 h、3 d、5 d、7 d 以及非 AKI 组在入院后 12 h、24 h、48 h、3 d、5 d、7 d Cys C 水平明显高于对照组(P<0.05),AKI 组基本在入院后 3 d 升至峰值,而后开始缓慢下降,且 AKI 组在入院后 12 h 的 Cys C 水平便开始明显高于非 AKI 组(P<0.05),详见表 1。

3 讨论

百草枯是一种非选择性除草剂,如果短时间摄入大量百草枯就会导致中毒,毒性可导致多器官功能严重损害,其中急性肾损伤是常见并发症,病死率高达 50%~70%^[7,8],因此早期评价患者中毒程度并且采取干预措施可以挽救患者生命及避免严重并发症或者后遗症的发生。早期干预 AKI 有助于防止病情进一步加重形成肾衰竭^[9]。百草枯口服或经皮肤中毒后并不会在机体内进行转化,一般在 48 h 内会经肾与肠道排出大部分^[10]。有研究表明,百草枯中毒后发生肾损伤的时间早于肺部症状^[11]。肾脏作为排泄百草枯的主要器官,虽然百草枯的排泄和肌酐没有明显的关系,但肌酐清除率越低,百草枯的排泄量也会越少,因此维持百草枯中毒患者正常的肾功能显得十分重要^[12]。

Scr 是肌肉在人体内代谢的产物,主要由肾小球滤过排出体外,各种肾脏炎症时均降低肾小球滤过率,Scr 可能升高,并测定血肌酐值作为追踪观察的指标^[13]。当 Scr 表现出异常高水平时,肾损害此时往往已处于比较严重的阶段^[14],因此极有必要积极寻找更早期的肾损害生物学指标。本文研究显示百草枯中毒患者 Scr 水平高于正常者,并且中毒患者发生 AKI 者 Scr 水平高于未发生 AKI 者,说明肾损伤越严重,Scr 水平越高。NGAL 是脂质运载蛋白的一种,是小分子量分泌性蛋白^[15],研究发现诊断急性肾损伤的最有效生物学标志是 NGAL^[16],尿 NGAL 在肾小管损害中能够高表达,且能较早地在尿液中被检测到^[17]。本研究中 AKI 组基本至入院后 2 h、非 AKI 组在入院后 8 h 的 NGAL 水平便明显高于正常值,在入院后 48 h 升至

表 1 病例组与对照组血清 CysC、NGAL 及 Scr 水平比较

Table 1 Comparison of serum CysC, NGAL and Scr levels in the case group and the control group

Time	Group	Cys C(mg/L)	NGAL(μ g/L)	Scr(μ mol/L)
After 15min	Control Group	0.77 $\pm$ 0.24	4.23 $\pm$ 1.15	56.78 $\pm$ 8.97
	AKI group	0.65 $\pm$ 0.07	4.45 $\pm$ 2.27	57.96 $\pm$ 12.78
	Non-AKI group	0.64 $\pm$ 0.13	4.26 $\pm$ 1.17	58.23 $\pm$ 9.38
2h	AKI group	0.72 $\pm$ 0.17	96.36 $\pm$ 26.29**	57.46 $\pm$ 10.17
	Non-AKI group	0.69 $\pm$ 0.52	4.35 $\pm$ 1.18	58.38 $\pm$ 11.45
4h	AKI group	0.83 $\pm$ 0.33	108.47 $\pm$ 61.65**	57.28 $\pm$ 13.28
	Non-AKI group	0.77 $\pm$ 0.42	4.23 $\pm$ 2.19	57.40 $\pm$ 12.68
8h	AKI group	1.66 $\pm$ 0.39*	215.45 $\pm$ 54.64**	67.39 $\pm$ 16.29*
	Non-AKI group	0.81 $\pm$ 0.63	6.23 $\pm$ 1.12*	68.52 $\pm$ 13.38*
12h	AKI group	2.11 $\pm$ 0.94**	275.34 $\pm$ 66.56**	90.43 $\pm$ 11.29**
	Non-AKI group	1.21 $\pm$ 0.64*	12.45 $\pm$ 5.23*	79.78 $\pm$ 12.47*
24h	AKI group	2.66 $\pm$ 0.73**	393.48 $\pm$ 77.68**	163.43 $\pm$ 36.69**
	Non-AKI group	1.53 $\pm$ 0.59*	52.45 $\pm$ 9.21*	80.78 $\pm$ 12.57*
48h	AKI group	3.13 $\pm$ 0.75**	433.39 $\pm$ 101.49**	256.68 $\pm$ 42.45**
	Non-AKI group	1.73 $\pm$ 0.79*	72.34 $\pm$ 8.34*	78.39 $\pm$ 9.59*
3d	AKI group	3.99 $\pm$ 1.03**	336.26 $\pm$ 95.19**	324.38 $\pm$ 29.68**
	Non-AKI group	1.84 $\pm$ 0.74*	88.18 $\pm$ 12.27*	79.45 $\pm$ 10.63*
5d	AKI group	3.77 $\pm$ 1.05**	308.27 $\pm$ 67.19**	286.19 $\pm$ 35.28**
	Non-AKI group	1.67 $\pm$ 0.69*	72.27 $\pm$ 12.17*	77.45 $\pm$ 18.67*
7d	AKI group	3.07 $\pm$ 0.66**	304.27 $\pm$ 21.46**	248.75 $\pm$ 35.28**
	Non-AKI group	1.36 $\pm$ 0.35*	68.15 $\pm$ 7.37*	74.23 $\pm$ 12.17*

Note: Compared with normal control group, *P<0.05; Compared with non AKI group, **P<0.05

峰值,而后开始缓慢下降,且 AKI 组入院后 4 h 的 NGAL 水平便开始明显高于非 AKI 组,比 Scr 的异常出现(18h)早出很多,这提示尿 NGAL 具有早期诊断 AKI 的临床价值。

CysC 主要分布于有核细胞和体液中,低分子量,对半胱氨酸蛋白酶具有抑制性^[18]。CysC 经过肾脏而被清除,反映肾小球滤过率变化的内源性标志物,并在近曲小管重吸收,但重吸收后被完全代谢分解,不返回血液^[19-20],由此得出血中浓度不依赖任何外来因素,主要由肾小球滤过决定,因此可以作为反映肾小球滤过情况的重要指标,血清 CysC 对于早期肾损害的敏感性要比 Scr 高出很多,且稳定性佳,一般不会受到性别、年龄、炎症等因素的干扰。本研究结果显示,AKI 组基本在入院后 8 h、非 AKI 组在入院后 12 h 的 Cys C 水平便明显高于正常值,AKI 组在入院后 3 d 升至峰值,而后开始缓慢下降,且 AKI 组在入院后 12 h 的 Cys C 水平便开始明显高于非 AKI 组,这提示血清 Cys C 变化与 AKI 早期病理进展具有较一致的同步性。

综上,血清 CysC 及尿 NGAL 水平在百草枯中毒后短时间内会出现异常升高,对早期诊断 AKI 具有积极意义。

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