

doi: 10.13241/j.cnki.pmb.2018.13.031

不同严重程度缺氧缺血性脑病患儿血清 MMP-9、MMP-2、UA 水平的表达及临床意义*

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摘要 目的: 研究不同严重程度缺氧缺血性脑病患儿血清基质金属蛋白酶-9(MMP-9)、基质金属蛋白酶-2(MMP-2)、尿酸(UA)水平的表达及临床意义。**方法:** 选取2015年4月-2017年4月本院收治的缺氧缺血性脑病患儿50例记为研究组,另取同期本院健康新生儿50例记为对照组,分别比较两组新生儿血清MMP-9、MMP-2及UA水平,对比研究组不同时期不同严重程度患儿血清MMP-9、MMP-2及UA水平,采用Preason相关性分析缺氧缺血性脑病病情严重程度与血清MMP-9、MMP-2、UA水平的关系。**结果:** 研究组患儿发病后1d、发病后3d、发病后7d血清MMP-9、MMP-2及UA水平均明显高于对照组,差异有统计学意义($P<0.05$),且MMP-9水平先升高后降低,MMP-2、UA水平呈逐渐升高的趋势($P<0.05$)。轻度组、中度组、重度组患儿发病后3d的MMP-9、MMP-2、UA水平高于发病后1d,且随着病情的加重,呈逐渐上升的趋势,差异有统计学意义($P<0.05$)。经Preason相关性分析可得:缺氧缺血性脑病病情严重程度与血清MMP-9、MMP-2、UA水平均呈正相关($P<0.05$)。**结论:** 缺氧缺血性脑病患儿随着病情的逐渐加重,其血清MMP-9、MMP-2及UA水平不断升高,呈正相关关系。

关键词: 缺氧缺血性脑病;新生儿;基质金属蛋白酶-9;基质金属蛋白酶-2;尿酸

中图分类号: R722 **文献标识码:** A **文章编号:** 1673-6273(2018)13-2550-04

Expression and Clinical Significance of Serum MMP-9, MMP-2 and UA in Neonates with Hypoxic Ischemic Encephalopathy with Different Severity*

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ABSTRACT Objective: To study the expression and clinical significance of serum matrix metalloproteinase-9 (MMP-9), matrix metalloproteinase-2 (MMP-2) and uric acid (UA) in neonates with hypoxic ischemic encephalopathy with different severity. **Methods:** 50 neonates with hypoxic ischemic encephalopathy who were treated in our hospital from April 2015 to April 2017 were selected as study group, at the same time, 50 healthy neonates in our hospital were selected and recorded as control group. The levels of serum MMP-9, MMP-2 and UA were compared between the two groups, the levels of serum MMP-9, MMP-2 and UA in neonates with different severity in study group at different stages were compared, and the relationship between the severity of hypoxic ischemic encephalopathy and the levels of serum MMP-9, MMP-2 and UA was analyzed by Preason correlation. **Results:** The levels of serum MMP-9, MMP-2 and UA of study group 1d after onset, 3d after onset, 7d after onset were significantly higher than the control group($P<0.05$), and the level of MMP-9 was increased first and then decreased, and the levels of MMP-2 and UA were increased gradually ($P<0.05$). The levels of MMP-9, MMP-2 and UA in the mild, moderate and severe group 3d after onset were higher than that of 1d after onset, with the aggravation of the disease, the trend was gradually rising, and the difference was statistically significant ($P<0.05$). The Preason correlation analysis showed that the severity of hypoxic ischemic encephalopathy was positively correlated with the levels of serum MMP-9, MMP-2 and UA ($P<0.05$). **Conclusion:** The levels of serum MMP-9, MMP-2 and UA in neonates with hypoxic-ischemic encephalopathy are increased with the gradual increase of the condition, and there is a positive correlation.

Key words: Hypoxic ischemic encephalopathy; Neonate; Matrix metalloproteinase-9; Matrix metalloproteinase-2; Uric acid

Chinese Library Classification(CLC): R722 **Document code:** A

Article ID: 1673-6273(2018)13-2550-04

前言

新生儿缺氧缺血性脑病主要是由于多种原因共同作用导致缺氧、脑血流量减少,从而引发新生儿脑损伤的一种病变,亦

是新生儿窒息的严重并发症之一^[1,2]。病情严重者普遍留有后遗症,包括智力低下、癫痫、视力障碍以及脑性瘫痪等,对患儿的正常生长发育以及生存质量造成了极大的威胁^[3-5]。因此,寻找一种早期有效的诊断方式以判断缺氧缺血性脑病患儿的病情

* 基金项目:海南省自然科学基金项目(211195)

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(收稿日期:2017-12-27 接受日期:2018-01-23)

严重程度显得尤为重要,并且有利于临床治疗方案的制定。而随着相关研究的不断深入,越来越多的学者发现基质金属蛋白酶-9(matrix metalloproteinase -9,MMP-9)、基质金属蛋白酶-2(matrix metalloproteinase -2,MMP-2)及尿酸(uric acid,UA)水平均与脑部损伤存在密切相关,开始受到广泛关注^[6-8]。鉴于此,本文通过研究不同严重程度新生儿缺氧缺血性脑病患儿血清MMP-9、MMP-2及UA水平的表达及临床意义并予以分析,旨在为临床诊治提供数据支持,现作以下报道。

1 资料与方法

1.1 一般资料

选取2015年4月-2017年4月本院收治的缺氧缺血性脑病新生儿50例记为研究组。纳入标准^[9]:(1)所有患儿均与2005中华医学会儿科分会新生儿学组制定的相关诊断标准相符;(2)所有患儿出生时均存在重度窒息以及原始反射异常、惊厥等神经系统症状;(3)均于发病24h内入院接受治疗。排除标准:(1)存在电解质紊乱以及颅内出血等因素导致的抽搐者;(2)合并宫内感染、遗传代谢性疾病以及其他先天性疾病所导致的脑损伤者;(3)伴有肝、肾等脏器功能严重障碍者;(4)合并血液系统疾病或恶性肿瘤疾病者。其中男性患儿29例,女性患儿21例,日龄1-14d,平均(4.51±0.52)d;根据病情严重程度将研究组患儿分为:轻度组22例,中度组18例,重度组10例。另取同期本院健康新生儿50例记为对照组。其中男性27例,女性23例,日龄1-12d,平均日龄(4.79±0.58)d。研究组与对照组新生儿性别、年龄比较,差异无统计学意义($P>0.05$),存在可比性。新生儿父母均签署了知情同意书,我院伦理委员会已批准同意。

1.2 研究方法

对照组新生儿于出生后1d,研究组新生儿与发病后1d、3d

以及7d时分别采集其清晨空腹静脉血5mL,以3000 r/min离心10 min,取上层血清保存于-80℃冰箱中待检。检测指标包括MMP-9、MMP-2及UA,采用酶联免疫吸附法检测MMP-9、MMP-2水平,采用日本奥林巴斯全自动生化分析仪进行检测UA水平,具体操作严格按照试剂盒说明书进行,相关试剂盒均购自上海酶联科技有限公司。

1.3 观察指标

分别比较研究组新生儿发病后不同时期与对照组新生儿的血清MMP-9、MMP-2及UA水平,并对比研究组不同时期不同严重程度患儿血清MMP-9、MMP-2及UA水平,采用Preason相关性分析缺氧缺血性脑病病情严重程度与血清MMP-9、MMP-2、UA水平的关系。

1.4 统计学方法

本研究数据均采用SPSS20.0软件进行检测分析,计数资料以[n(%)]表示,实施 χ^2 检验计量资料以($\bar{x}\pm s$)表示,实施t检验,多组间比较予以单因素方差分析,缺氧缺血性脑病病情严重程度与血清MMP-9、MMP-2、UA水平的关系予以Preason相关性分析,检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 研究组发病后不同时期与对照组新生儿血清MMP-9、MMP-2及UA水平对比

研究组发病后不同时期与对照组新生儿血清MMP-9、MMP-2及UA水平整体比较差异有统计学意义($P<0.05$),研究组患儿发病后1d、发病后3d、发病后7d血清MMP-9、MMP-2及UA水平均明显高于对照组,差异有统计学意义($P<0.05$),且MMP-9水平先升高后降低,MMP-2、UA水平呈逐渐升高的趋势($P<0.05$)。见表1。

表1 研究组发病后不同时期与对照组新生儿血清MMP-9、MMP-2及UA水平对比($\bar{x}\pm s$)

Table 1 Comparison of serum MMP-9, MMP-2 and UA levels in neonates between the study group and the control group at different stages after onset($\bar{x}\pm s$)

Groups	n	MMP-9(ng/mL)	MMP-2(ng/mL)	UA(μ mol/L)
Control group	50	112.40±38.84	135.68±58.17	72.59±12.47
Study group	1d after onset	487.25±321.52 [△]	654.32±391.50 [△]	211.50±98.38 [△]
	3d after onset	713.50±291.58 ^{△#}	952.10±401.28 ^{△#}	386.42±161.30 ^{△#}
	7d after onset	430.76±301.17 ^{△*}	1067.32±428.19 ^{△#}	410.58±149.11 ^{△#}
F	-	6.321	12.493	9.036
P	-	0.000	0.000	0.000

Note: compared with the control group, [△] $P<0.05$; compared with 1d after onset, [#] $P<0.05$; compared with 3d after onset, ^{*} $P<0.05$.

2.2 研究组不同时期不同严重程度患儿血清MMP-9、MMP-2及UA水平对比

轻度组、中度组、重度组患儿发病后1d、发病后3d的MMP-9、MMP-2、UA水平比较有统计学差异($P<0.05$),三组患儿发病后3d的MMP-9、MMP-2、UA水平高于发病后1d,且随着病情的加重,呈逐渐上升的趋势,差异有统计学意义($P<0.05$)。见表2。

2.3 缺氧缺血性脑病病情严重程度与血清MMP-9、MMP-2、

UA水平的相关性分析

经Preason相关性分析可得:缺氧缺血性脑病病情严重程度与血清MMP-9、MMP-2、UA水平均呈正相关($P<0.05$)。见表3。

3 讨论

新生儿缺氧缺血性脑病属于围产期缺氧窒息引发的一种缺氧缺血性损害,在围产期神经系统疾病中占据重要位置^[10-12]。

表 2 研究组不同时期不同严重程度患儿血清 MMP-9、MMP-2 及 UA 水平对比($\bar{x} \pm s$)

Table 2 Comparison of serum MMP-9, MMP-2 and UA levels in neonates with different severity in the study group at different stages ($\bar{x} \pm s$)

Groups	n	MMP-9(ng/mL)		MMP-2(ng/mL)		UA(μmol/L)	
		1d after onset	3d after onset	1d after onset	3d after onset	1d after onset	3d after onset
Mild group	22	257.14± 132.95	407.48± 70.92 ^a	467.30± 178.74	587.32± 91.56 ^a	153.25± 76.32	254.32 ± 77.32 ^a
Medium group	18	638.27± 261.30 [#]	910.53± 132.50 [#]	965.32± 308.17 [#]	1135.23± 240.15 [#]	211.57± 97.51 [#]	344.31 ± 51.37 [#]
Severe group	10	937.43± 182.45 ^{#*}	1077.62± 155.30 ^{#*}	1289.53± 320.59 ^{#*}	1418.52± 422.83 ^{#*}	312.76± 135.39 ^{#*}	452.43 ± 123.59 ^{#*}
F	-	8.932	14.302	11.053	12.462	7.956	17.411
P	-	0.000	0.000	0.000	0.000	0.000	0.000

Note: compared with 1d after onset, ^a $P<0.05$; compared with mild group, [#] $P<0.05$; compared with moderate group, ^{*} $P<0.05$.

表 3 缺氧缺血性脑病病情严重程度与血清 MMP-9、MMP-2、UA 水平的相关性分析

Table 3 Correlation analysis between the severity of hypoxic ischemic encephalopathy and the levels of serum MMP-9, MMP-2 and UA

Related indicators	Severity of hypoxic-ischemic encephalopathy	
	r	P
MMP-9	0.583	0.001
MMP-2	0.503	0.012
UA	0.612	0.000

该患儿主要临床症状表现包括意识障碍、中枢性呼吸衰竭以及肌张力低下等^[13-15]。根据患者病情严重程度不同可分为轻、中、重三种,且轻度患儿 24h 内主要以兴奋症状为主,随后逐渐减轻,不伴有意识障碍;中度患儿则存在嗜睡以及肌张力低下,约有 1/2 患儿伴有惊厥;重度患儿则以抑制症状为主,表现为昏迷、呼吸暂停等,具有较高的病死率,存活患儿普遍留有严重的后遗症^[16-18]。由此,如何对新生儿缺氧缺血性脑病进行早期有效的诊断显得尤为重要,有利于为临床治疗方案的制定提供指导作用,进一步达到改善患儿预后的目的。

本研究结果发现:研究组患儿发病后 1d、发病后 3d、发病后 7d 血清 MMP-9、MMP-2 及 UA 水平均明显高于对照组($P<0.05$),且 MMP-9 水平先升高后降低,MMP-2、UA 水平呈逐渐升高的趋势。说明缺氧缺血性脑病患者血清 MMP-9、MMP-2 及 UA 水平存在明显高表达,可能是因为发病后 1d 处于急性期,发病后 3d 处于高峰期,发病后 7d 处于恢复期,沈德新等^[19]人的研究报道也可以加以佐证。MMP-9 与 MMP-2 均属于明胶酶家族成员之一,两者对内皮细胞基膜具有一定的分解破坏作用,同时具有调节其他蛋白酶与细胞因子活性的作用,可在炎症反应、血管病变以及肿瘤疾病中发生一定程度的变化,且对患者神经系统以及细胞外基质产生一定影响,进一步导致血脑屏障出现损害,最后导致神经元以及脑细胞出现损伤^[20-22]。UA 作为嘌呤核苷酸代谢的终末产物,其血清水平主要是通过嘌呤分解速度以及肾脏排泄功能强弱决定的,是临床上广泛用于反映氧自由基代谢情况的敏感指标之一,其水平高低可直接反映组织缺氧缺血的变化^[23,24]。且有研究报道显示,缺氧缺血性脑病

可通过黄嘌呤氧化酶途径分泌大量氧自由基,并在组织缺血、缺氧状态下,次黄嘌呤自身无法代谢,从而被催化成黄嘌呤以及 UA,进一步导致大量的自由基产生^[25,26]。此外,三组患儿发病后 3d 的 MMP-9、MMP-2、UA 水平高于发病后 1d,且随着病情的加重,呈逐渐上升的趋势($P<0.05$),这表明了随着缺氧缺血性脑病患者病情逐渐加重,血清 MMP-9、MMP-2 及 UA 水平相应升高,提示了上述三项血清学指标对判断缺氧缺血性脑病的严重程度以及预后具有重要意义。究其原因,笔者认为在 UA 的生成过程中,随着氧自由基的分泌增多,炎症递质的产生也不断增加,进一步促使内皮功能出现损伤,从而加重了患儿病情^[27,28];MMP-9 与 MMP-2 则可对微血管基底膜造成破坏,进一步对内皮功能造成损伤,导致通透性的增加,最终加重了组织缺氧缺血情况^[29,30]。经 Preason 相关性分析可得:缺氧缺血性脑病病情严重程度与血清 MMP-9、MMP-2、UA 水平均呈正相关($P<0.05$)。这也再次证实了上述三项指标在缺氧缺血性脑病的发生、发展过程中可能存在着协同作用。临床工作中可通过对上述指标水平进行检测,从而对缺氧缺血性脑病的严重程度判断以及近期预后提供参考依据。

综上所述,缺氧缺血性脑病患者血清 MMP-9、MMP-2 及 UA 水平存在明显高表达,且上述指标表达水平越高,患儿病情越严重。临床上可通过联合检测上述血清学指标,从而有效判断缺氧缺血性脑病患者的病情严重程度。这也为临床治疗以及预后评估提供了新的靶点和思路。

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