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川崎病患儿血浆中可溶性内皮细胞蛋白 C 受体、一氧化氮的表达 及与炎症反应和冠状动脉病变的关系 *

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摘要 目的:研究川崎病患儿血浆中可溶性内皮细胞蛋白 C 受体(sEPCR)、一氧化氮(NO)的表达及与炎症反应和冠状动脉病变(CAL)的关系。**方法:**选择 2016 年 12 月至 2018 年 2 月盘锦市中心医院收治的川崎病患儿 104 例为川崎病组,根据患儿彩色超声心动图检测结果将川崎病组分为 CAL 组 30 例和非 CAL 组(NCAL 组)74 例。另选取同期于我院进行体检的健康儿童 56 例为对照组。比较川崎病组与对照组、川崎病组患儿急性期与缓解期、CAL 组与 NCAL 组 sEPCR、NO、C-反应蛋白(CRP)、白细胞介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)水平,并分析川崎病患儿 sEPCR、NO 与炎症因子及 CAL 的相关性。**结果:**川崎病组患儿 sEPCR、NO、CRP、IL-6、TNF- α 水平均高于对照组,差异有统计学意义($P<0.05$)。川崎病组患儿急性期 sEPCR、NO、CRP、IL-6、TNF- α 水平均高于缓解期,差异有统计学意义($P<0.05$)。CAL 组 sEPCR、NO、CRP、IL-6、TNF- α 水平均高于 NCAL 组,差异有统计学意义($P<0.05$)。经 Pearson 相关性分析结果显示,川崎病患儿 sEPCR、NO 与 CRP、IL-6、TNF- α 及 CAL 均呈正相关($P<0.05$)。**结论:**川崎病患儿 sEPCR、NO 水平与炎症因子及 CAL 相关,sEPCR、NO 可能在其炎症反应及 CAL 进展中起到一定的作用。

关键词:川崎病;儿童;可溶性内皮细胞蛋白 C 受体;一氧化氮;炎症反应;冠状动脉病变;关系

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Expression of Plasma Soluble Endothelial Protein C Receptor and Nitric Oxide in Children with Kawasaki Disease and its Relationship with Inflammatory Reaction and Coronary Artery Disease*

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ABSTRACT Objective: To study the expression of plasma soluble endothelial protein C receptor (sEPCR) and nitric oxide (NO) in children with Kawasaki disease and its relationship with inflammatory reaction and coronary artery disease(CAL). **Methods:** 104 children with Kawasaki disease who were treated in Central Hospital of Panjin from December 2016 to February 2018 were selected as Kawasaki disease group, according to the results of color echocardiography, the children of Kawasaki disease group were divided into CAL group with 30 cases and non CAL group (NCAL group) with 74 cases. In addition, 56 healthy children who were received healthy physical examination in our hospital at the same time were selected as the control group. The levels of sEPCR, NO, C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) were compared between the Kawasaki disease group and the control group, the acute stage and remission stage of children in the Kawasaki disease group, the CAL group and the NCAL group. The correlation of sEPCR, NO and inflammatory factors, CAL of Kawasaki disease were analyzed. **Results:** The levels of sEPCR, NO, CRP, IL-6, TNF- α of Kawasaki disease group were higher than the control group, the difference was statistically significant ($P<0.05$). The levels of sEPCR, NO, CRP, TNF- α , IL-6 in acute stage of Kawasaki disease group were higher than those in remission stage, the difference was statistically significant ($P<0.05$). The levels of sEPCR, NO, CRP, TNF- α and IL-6 in CAL group were higher than those in NCAL group, and the difference was statistically significant ($P<0.05$). The results of Pearson correlation analysis showed that sEPCR and NO were positively correlated with CRP, IL-6, TNF- α and CAL in children with Kawasaki disease ($P<0.05$). **Conclusion:** The levels of sEPCR and NO in children with Kawasaki disease are related to inflammatory factors and CAL, sEPCR and NO may play a certain role in its inflammatory response and CAL progression.

Key words: Kawasaki disease; Children; Soluble endothelial cell protein C receptor; Nitric oxide; Inflammatory reaction; Coronary

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前言

川崎病是一种以全身血管炎以及变态免疫为病理特征的急性发热出疹性疾病,好发于出生后3个月至5岁的婴幼儿,在成人中比较少见,临床多表现为皮疹、发热、手足硬性水肿、淋巴结肿大以及口腔粘膜充血等^[1-3]。川崎病患者早期病理表现为全身微血管炎症,患病两周后将出现动脉内膜炎和动脉周围炎^[4,5]。冠状动脉病变(Coronary artery lesion, CAL)是川崎病的主要并发症之一,其可进展为冠状动脉狭窄及冠状动脉炎症反应,严重时将导致冠状动脉瘤的形成,甚至造成患儿猝死,威胁着患儿的生命健康安全^[6,8]。可溶性内皮细胞蛋白C受体(Soluble endothelial cell protein C receptor, sEPCR)主要存在于血浆中,是由EPCR在金属蛋白酶的作用下与细胞膜分离并脱落于血浆中而形成的,是机体炎症时血管损伤的重要生物标记物^[9]。一氧化氮(Nitric oxide, NO)是一种新型生物分子,其具有扩张血管的功能,在心血管系统中起到重要的调节作用,是内皮细胞功能的生物标志物之一^[10]。有报道显示^[11,12],sEPCR、NO在心血管类及炎症性疾病患者中均过度表达,其参与了疾病的发生、发展。鉴于此,本研究通过探讨sEPCR、NO与川崎病患者炎症反应及CAL的关系,以进一步验证sEPCR、NO在川崎病的作用,以为临床诊治提供参考与数据支持,阐述结果如下。

1 资料与方法

1.1 一般资料

选择2016年12月至2018年2月盘锦市中心医院收治的川崎病患者104例为川崎病组,纳入标准:(1)所有患儿均符合第七次世界小儿川崎病研讨会(日本Hahone,2002修订第5版)川崎病诊断标准^[13];(2)发热天数 ≥ 5 天;(3)患儿家属对本研究知情同意并签署知情同意书。排除标准:(1)入组前使用过丙种球蛋白、激素、阿司匹林等药物者;(2)临床资料不全者;(3)伴有心脏疾病者。104例川崎病患者中男72例,女32例;年龄3

个月-5岁,平均 (2.56 ± 0.98) 岁;体质量指数(Body mass index, BMI)为12-18 kg/m²,平均 (15.34 ± 2.39) kg/m²。对所有患儿行彩色超声心动图检测,根据检测结果将患儿分为CAL组30例和非CAL组(NCAL组)74例。另选取同期于我院进行体检的健康儿童56例为对照组,其中男38例,女18例;年龄4个月-6岁,平均 (2.77 ± 0.85) 岁;BMI为13-18 kg/m²,平均 (15.84 ± 2.02) kg/m²。川崎病组和对照组性别比例、年龄构成、BMI比较差异无统计学意义($P > 0.05$),均衡可比。本研究获得辽宁省盘锦市中心医院伦理委员会的批准。

1.2 方法

于川崎病组患儿急性期(入院24 h内)和缓解期(体温恢复正常1周内)、对照组儿童在进行健康检查时,分别抽取所有受试者晨起空腹静脉血3 mL,立刻置于4℃含枸橼酸钠抗凝液的试管中,以3500 r/min的速率离心10 min,分离血浆,保存于-20℃的冰箱中冷冻,待测。采用酶联免疫吸附法(试剂盒购自上海森雄科技实业有限公司)检测C-反应蛋白(C-reactive protein, CRP)、sEPCR、白细胞介素-6(Interleukin -6, IL-6)、肿瘤坏死因子- α (Tumor necrosis factor- α , TNF- α)水平,采用硝酸还原酶法(试剂盒购自南京建成生物公司)检测NO水平。

1.3 统计学方法

所有数据均用SPSS19.0进行统计分析,性别比例等计数资料以率(%)的形式表示,采用 χ^2 检验,炎症因子、sEPCR、NO水平等计量资料以均值 $\pm$ 标准差($\bar{x} \pm s$)的形式表示,采用t检验。采用Pearson相关性分析方法分析川崎病患者sEPCR、NO与CRP、IL-6、TNF- α 及CAL的相关性。检验标准设置为 $\alpha = 0.05$ 。

2 结果

2.1 川崎病组与对照组sEPCR、NO及炎症因子水平比较

川崎病组患儿sEPCR、NO、CRP、IL-6、TNF- α 水平均高于对照组,差异有统计学意义($P < 0.05$)。见表1。

表1 川崎病组与对照组sEPCR、NO、CRP、IL-6、TNF- α 水平比较($\bar{x} \pm s$)

Table 1 Comparison of sEPCR, NO, CRP, IL-6, TNF- α levels in Kawasaki disease group and control group($\bar{x} \pm s$)

Groups	n	sEPCR(ng/mL)	NO(μ mol/L)	CRP(mg/L)	IL-6(pg/mL)	TNF- α (ng/L)
Kawasaki disease group	104	12.34 $\pm$ 3.98	38.76 $\pm$ 22.56	108.77 $\pm$ 53.12	214.56 $\pm$ 40.45	36.56 $\pm$ 7.99
Control group	56	6.01 $\pm$ 1.97	25.24 $\pm$ 15.48	2.98 $\pm$ 1.04	42.09 $\pm$ 14.70	15.69 $\pm$ 5.23
t		11.176	4.003	14.880	30.793	17.607
P		0.000	0.000	0.000	0.000	0.000

2.2 川崎病组患儿急性期与缓解期sEPCR、NO及炎症因子水平比较

川崎病组患儿急性期sEPCR、NO、CRP、IL-6、TNF- α 水平均高于缓解期,差异有统计学意义($P < 0.05$)。见表2。

2.3 CAL组与NCAL组sEPCR、NO及炎症因子水平比较

CAL组sEPCR、NO、CRP、IL-6、TNF- α 水平均高于NCAL组,差异有统计学意义($P < 0.05$)。见表3。

2.4 川崎病患者sEPCR、NO与炎症因子及CAL的关系

经Pearson相关性分析结果显示,川崎病患者sEPCR、NO与CRP、IL-6、TNF- α 及CAL均呈正相关($P < 0.05$)。见表4。

3 讨论

川崎病又被称为小儿皮肤黏膜淋巴结综合征,是1967年由日本儿科医生川崎富作首次报道,并以其名字命名的一种疾

病,近年来,在发达及多数发展中国家,川崎病发病率具有增加的趋势^[14,15]。川崎病对心脏的危害主要表现为 CAL、心肌内膜炎以及心肌炎等,其中以 CAL 的危害最大,其已成为导致川崎病患儿死亡的主要因素,对患儿的生存质量造成严重影响^[16,17]。截至目前,川崎病病因及发病机制还未明确,有报道显示^[18],在患儿

急性期常因免疫系统异常活化,从而释放出大量的炎症因子,导致炎症因子过度表达,进而引发血管内皮炎症损伤,促进了该病的发生与发展,因此,分析川崎病患儿中炎症因子的表达对疾病的控制具有重要的意义。

表 2 川崎病组患儿急性期与缓解期 sEPCR、NO、CRP、IL-6、TNF- α 水平比较($\bar{x} \pm s$)

Table 2 Comparison of sEPCR, NO, CRP, IL-6, TNF- α levels in acute stage and remission of children in Kawasaki disease group($\bar{x} \pm s$)

Groups	n	sEPCR(ng/mL)	NO(μ mol/L)	CRP(mg/L)	IL-6(pg/mL)	TNF- α (ng/L)
Acute stage	104	15.94 $\pm$ 3.76	46.22 $\pm$ 24.03	211.45 $\pm$ 56.90	366.14 $\pm$ 39.68	58.12 $\pm$ 7.44
Remission stage	104	9.55 $\pm$ 1.78	30.78 $\pm$ 16.09	4.99 $\pm$ 1.56	66.74 $\pm$ 15.20	20.80 $\pm$ 5.26
t		15.665	5.445	36.989	71.856	41.770
P		0.000	0.000	0.000	0.000	0.000

表 3 CAL 组与 NCAL 组 sEPCR、NO、CRP、IL-6、TNF- α 水平比较($\bar{x} \pm s$)

Table 3 Comparison of sEPCR, NO, CRP, IL-6, TNF- α levels between CAL group and NCAL group($\bar{x} \pm s$)

Groups	n	sEPCR(ng/mL)	NO(μ mol/L)	CRP(mg/L)	IL-6(pg/mL)	TNF- α (ng/L)
CAL group	30	17.33 $\pm$ 3.23	55.34 $\pm$ 23.95	126.34 $\pm$ 60.12	232.80 $\pm$ 43.12	38.90 $\pm$ 8.34
NCAL group	74	8.68 $\pm$ 1.90	29.05 $\pm$ 13.47	88.89 $\pm$ 57.56	189.67 $\pm$ 44.89	28.77 $\pm$ 7.98
t		16.964	7.097	2.968	4.489	5.790
P		0.000	0.000	0.004	0.000	0.000

表 4 川崎病患儿 sEPCR、NO 与 CRP、IL-6、TNF- α 及 CAL 的关系分析

Table 4 Analysis of the relationship between sEPCR, NO and CRP, IL-6, TNF- α , CAL in children with Kawasaki disease

Indexes	CRP		IL-6		TNF- α		CAL	
	r	P	r	P	r	P	r	P
sEPCR	0.390	0.021	0.454	0.032	0.473	0.005	0.504	0.008
NO	0.385	0.000	0.597	0.000	0.428	0.006	0.369	0.000

本研究中,川崎病组患儿 sEPCR、NO、CRP、IL-6、TNF- α 水平平均高于对照组,川崎病组患儿急性期 sEPCR、NO、CRP、IL-6、TNF- α 水平高于缓解期,CAL 组 sEPCR、NO、CRP、IL-6、TNF- α 水平高于 NCAL 组,提示了川崎病患儿血浆中 sEPCR、NO 的表达及 CRP、IL-6、TNF- α 水平的变化与疾病发生与进展存在密切联系。CRP 是由肝细胞合成的一种急性时相蛋白,在免疫应答初期具有较强的敏感性,其水平的变化可以反映炎症的程度和细菌感染存在;同时,CRP 能抑制血小板激活因子的产生,从而刺激血小板的聚集,进而产生大量的炎症因子,最终造成血管的损伤^[19,20]。IL-6 是由纤维细胞、B 淋巴细胞、T 淋巴细胞等产生的炎症因子,其可通过激活和调节免疫细胞的活化、增殖和分化,并分泌自身抗体,引发内皮细胞毒性作用,进而导致内皮细胞损伤^[21,22]。TNF- α 是人体内主要的促炎因子,由单核巨噬细胞产生,同时其也可以产生于心肌细胞、血管内皮细胞以及血管平滑肌细胞等,在川崎病患儿急性期,TNF- α 可以直接损伤血管内皮细胞,进而导致血管损伤^[23,24]。sEPCR 是细胞膜结合 EPCR 之后释放入血浆中的一种存在形式,当血管内皮细胞受损时,EPCR 将与细胞膜脱离,从而进入血液循环系统,使得血浆中 sEPCR 水平迅速升高,因此其水平的高低可以有效的反映出心血管疾病的严重程度^[25,26]。NO 是一种气体分

子,其功能的失调将引发多种心血管疾病;同时 NO 也是一种细胞毒性分子,其与过氧离子结合产生的过氧亚硝基是具有广泛活性的化学物质,将导致血管细胞的损伤,但其具体发挥何种作用与其自身的作用部位、作用时间及水平有关,因此当川崎病患儿 NO 的表达增强时,其水平急速上升,导致其发挥毒性作用^[27,28]。另外,经 Pearson 相关性分析结果显示,川崎病患儿 sEPCR、NO 与 CRP、IL-6、TNF- α 及 CAL 均呈正相关,这再次证明 sEPCR、NO 可能参与了川崎病的进展,同时还说明 sEPCR、NO 可能是通过调节患儿炎症因子水平及加速其 CAL 进程,从而促进病情的进展。川崎病患儿在炎症因子的作用下,血管损伤早期就将发生血管功能障碍,当血流被阻断进而引起反应性充血时,在血流剪切应力的作用下,内皮细胞释放大量的 NO、sEPCR,从而引起平滑肌的松弛;而内皮细胞在炎症因子的持续刺激下,NO、sEPCR 将减少,进而导致血管舒张反应力降低,血流恢复正常,因此,在川崎病患儿中,NO、sEPCR 的表达与炎症反应及 CAL 存在密切联系^[29,30]。

综上所述,川崎病患儿 NO、sEPCR 异常表达,其可能通过调节炎症因子水平而参与了疾病的发生与发展,同时患儿 CAL 与 NO、sEPCR 异常表达密切相关,可以通过监测 NO、sEPCR 的表达以判断病情的严重程度。

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