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子痫前期患者血清 APN、TNF- α 、Apelin 水平的表达及相关性研究 *

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摘要 目的:探讨子痫前期患者血清脂联素(APN)、肿瘤坏死因子- α (TNF- α)、Apelin 水平的表达及相关性。方法:选取 2015 年 10 月到 2017 年 8 月在辽河油田总医院妇产科就诊的子痫前期患者 86 例,根据患者的病情严重程度将其分为轻度子痫前期组(46 例)和重度子痫前期组(40 例),另选取同期在我院进行产检的健康孕妇 40 例作为对照组,比较三组受试者血清中 APN、TNF- α 、Apelin、低密度脂蛋白胆固醇(LDL-C)、甘油三酯(TG)、高密度脂蛋白胆固醇(HDL-C)和总胆固醇(TC)水平,并分析子痫前期患者血清中 APN、TNF- α 、Apelin、LDL-C、TG、HDL-C、TC 的相关性。结果:重度子痫前期组血清中 APN 水平低于轻度子痫前期组和对照组, TNF- α 、Apelin 水平高于轻度子痫前期组和对照组 ($P<0.05$);轻度子痫前期组血清中 APN 水平低于对照组, TNF- α 、Apelin 水平高于对照组($P<0.05$)。重度子痫前期组血清中 LDL-C、TG、TC 水平高于轻度子痫前期组和对照组, HDL-C 水平低于轻度子痫前期组和对照组($P<0.05$);轻度子痫前期组 LDL-C、TC 水平高于对照组, HDL-C 水平低于对照组($P<0.05$)。Pearson 相关性分析结果显示,子痫前期患者血清中 APN 与 TNF- α 、Apelin、LDL-C、TG 呈负相关,与 HDL-C 呈正相关($P<0.05$);TNF- α 与 Apelin、LDL-C、TG、TC 呈正相关,与 HDL-C 呈负相关($P<0.05$);Apelin 与 LDL-C、TG、TC 呈正相关,与 HDL-C 呈负相关($P<0.05$)。结论:子痫前期患者血清中 APN 水平明显下降, TNF- α 、Apelin 明显升高,三种指标可相互影响,且均可影响机体的脂质代谢水平,共同调节子痫前期患者的疾病进展。

关键词:子痫前期;脂联素;肿瘤坏死因子- α ;Apelin

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Expression and Correlation of Serum APN, TNF- α and Apelin Levels in Patients with Preeclampsia*

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ABSTRACT Objective: To investigate the expression and correlation of serum adiponectin (APN), tumor necrosis factor- α (TNF- α) and Apelin levels in patients with preeclampsia. **Methods:** 86 patients with preeclampsia who were treated in obstetrics and gynecology department of Liaohe general hospital from October 2015 to August 2017 were selected. According to the severity of the patient's condition, they were divided into mild preeclampsia group (46 cases) and severe preeclampsia group (40 cases). In addition, 40 healthy pregnant women in our hospital during the same period were selected as control group. The levels of APN, TNF- α , Apelin, low density lipoprotein cholesterol (LDL-C), triglyceride (TG), high density lipoprotein cholesterol (HDL-C) and total cholesterol (TC) of subjects in three groups were compared, and the correlation of serum APN, TNF- α , Apelin, LDL-C, TG, HDL-C and TC in patients with preeclampsia was also analyzed. **Results:** The level of serum APN in severe preeclampsia group was lower than that in mild preeclampsia group and control group, the levels of TNF- α and Apelin were significantly higher than those in mild preeclampsia group and control group ($P<0.05$). The level of serum APN in mild preeclampsia group was lower than that in the control group, and the levels of TNF- α , Apelin were higher than that in the control group ($P<0.05$). The levels of serum LDL-C, TG and TC in severe preeclampsia group were higher than those in mild preeclampsia group and control group, the level of HDL-C was lower than that in mild preeclampsia group and control group ($P<0.05$). The levels of LDL-C and TC in the mild preeclampsia group were higher than that in the control group, and the level of HDL-C was lower than that of the control group ($P<0.05$). The results of Pearson correlation analysis showed that the serum APN in patients with preeclampsia was negatively correlated with TNF- α , Apelin, LDL-C and TG, and it was positively correlated with HDL-C ($P<0.05$). TNF- α was positively correlated with Apelin, LDL-C, TG and TC, and it was negatively correlated with HDL-C ($P<0.05$). Apelin was positively correlated with LDL-C, TG and TC, and it was negatively correlated with HDL-C ($P<0.05$). **Conclusion:** The ex-

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pression of serum APN in patients with preeclampsia is significantly decreased, and the expression of TNF- α and Apelin are significantly increased. The three indexes can affect each other, and they can affect the lipid metabolism level of the body, so as to regulate the disease progression in preeclampsia.

Key words: Preeclampsia; Adiponectin; Tumor necrosis factor- α ; Apelin

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前言

子痫前期是指孕妇在怀孕前血压正常,而在妊娠 20 周以后出现蛋白尿、高血压的现象,该病患者还会出现浮肿、头痛、眼花、抽搐等症状,是导致孕产妇和围产儿死亡的重要原因之一,严重影响孕产妇和围产儿的生命健康^[1-3]。子痫前期的发病机制尚未完全阐明,目前认为其可能与胎盘滋养细胞缺血、免疫调节功能异常、内皮细胞损伤、炎症反应、氧化应激、遗传等多种因素有关^[4-6],近年来内皮细胞损伤和炎症反应对子痫前期发病的促进作用得到了较多研究的证实^[7,8]。脂联素(Adiponectin, APN)是一种内源性生物活性多肽,主要由脂肪细胞分泌,具有抑制炎症反应、保护血管内皮细胞、改善胰岛素抵抗的作用^[9]。肿瘤坏死因子- α (Tumor necrosis factor- α , TNF- α)是一种多功能调节因子,参与了机体的免疫调节和炎症反应,同时其可以通过促进炎症反应来损伤内皮细胞^[10]。Apelin 是一种新型的生物活性肽,于 1998 年由 Tatemoto K 等人在牛胃的分泌物中发现,有研究证实^[11],Apelin 可调节内皮细胞功能。本研究通过探讨子痫前期患者血清 APN、TNF- α 、Apelin 水平的表达,并分析其相关性,旨在进一步研究内皮细胞损伤和

炎症反应在子痫前期发生、发展中的作用,报道如下。

1 资料与方法

1.1 一般资料

选取 2015 年 10 月到 2017 年 8 月在辽河油田总医院妇产科就诊的子痫前期患者 86 例,纳入标准:(1)所有患者均符合妇产科学(第 8 版)中关于子痫前期的诊断标准^[12],即:妊娠 20 周以后血压高于 140 mmHg/90 mmHg,并伴有蛋白 ≥ 0.3 g/24 h 或随机尿蛋白(+);(2)均为初次怀孕,且为单胎妊娠;(3)均为自然怀孕;(4)年龄在 20-40 岁范围内;(5)均为晚发型子痫前期。排除标准:(1)合并有恶性肿瘤者;(2)存在产科合并症者,如胎膜早破、胎盘早剥、前置胎盘、胎儿宫内发育受阻等;(3)存在严重感染和免疫性疾病者;(4)存在精神障碍者。根据患者的病情严重程度将其分为轻度子痫前期组(46 例)和重度子痫前期组(40 例),其判定标准参考妇产科学(第 8 版)中的相关规定^[12]。另选取同期在我院进行产检的健康孕妇 40 例作为对照组,入选者均为初次怀孕和自然怀孕,且为单胎妊娠。所有受试者对本研究均知情同意。三组受试者的一般资料比较无统计学差异($P>0.05$),见表 1。本院伦理委员会已批准本次研究。

表 1 三组受试者的一般资料比较($\bar{x} \pm s$)

Table 1 Comparison of general information of subjects in three groups($\bar{x} \pm s$)

Groups	n	Age(years old)	Gestational weeks (weeks)	Body mass index (kg/m ²)
Control group	40	27.54 $\pm$ 4.68	36.23 $\pm$ 1.24	26.21 $\pm$ 1.18
Mild preeclampsia group	46	26.61 $\pm$ 5.24	36.52 $\pm$ 1.03	26.58 $\pm$ 1.06
Severe preeclampsia group	40	26.89 $\pm$ 4.95	36.44 $\pm$ 1.15	26.74 $\pm$ 1.13
F		0.138	0.762	0.782
P		0.872	0.469	0.460

1.2 检验方法

抽取所有受试者的清晨空腹肘静脉血 5 mL,在 37℃ 下水浴 1 h,采用离心机(上海安亭科学仪器厂,型号:TDL-5-A)以 3000 r/min 的离心速度离心 10 min,分离血清,置于 -20℃ 的冰箱中保存。采用酶联免疫吸附法检测所有受试者血清中 APN、TNF- α 、Apelin 水平。分别设置标准孔、待测样品孔以及空白孔。分别在标准孔、待测样品孔中加入 100 μ L 标准品和待测样品,空白孔不作处理,封板后在 37℃ 下静置 60 min。倒去液体,每个孔内加入洗涤液洗涤,重复两次,拍干。每孔中加入 100 μ L 第一抗体工作液,轻微摇晃,混匀后封板,在 37℃ 下静置 60 min。倒去液体,每个孔内加入洗涤液反复洗涤,拍干。每孔中加入 100 μ L 酶标抗体工作液,封板后在 37℃ 下静置 30 min。倒去液体,每个孔内加入洗涤液洗涤,重复两次,拍干。每孔中加入 100 μ L 底物工作液,封板后在 37℃ 下静置 15 min。每孔中

加入 50 μ L 终止液,采用酶标仪(芬兰雷勃,型号:MK3)检测各孔在波长 450 nm 处的吸光度。以标准品浓度为横坐标,吸光度为纵坐标绘出标准曲线,计算样品浓度。APN、TNF- α 、Apelin 试剂盒均购于上海西唐生物科技有限公司。采用全自动生化分析仪(日立,型号:7600)检测所有受试者血清中的低密度脂蛋白胆固醇(Low density lipoprotein cholesterol, LDL-C)、甘油三酯(triglyceride, TG)、高密度脂蛋白胆固醇(High density lipoprotein cholesterol, HDL-C)和总胆固醇(total cholesterol, TC)的水平。

1.3 观察指标

比较三组受试者血清中 APN、TNF- α 、Apelin、LDL-C、TG、HDL-C、TC 的水平,并分析子痫前期患者血清中 APN、TNF- α 、Apelin、LDL-C、TG、HDL-C、TC 表达的相关性。

1.4 统计分析

采用 SPSS20.0 进行统计分析, APN、TNF- α 、Apelin 及血脂指标水平等计量资料采用均值 $\pm$ 标准差($\bar{x} \pm s$)的形式表示,三组间比较采用单因素方差分析,两两比较采用 LSD-t 检验。子痫前期患者 APN、TNF- α 、Apelin 及血脂指标间的相关性采用 Pearson 法进行分析。检验标准设置为 $\alpha=0.05$ 。

2 结果

表 2 三组受试者血清中 APN、TNF- α 、Apelin 水平比较($\bar{x} \pm s$, ng/L)

Table 2 Comparison of serum APN, TNF- α , Apelin levels of subjects in three groups ($\bar{x} \pm s$, ng/L)

Groups	n	APN	TNF- α	Apelin
Control group	40	12.86 $\pm$ 3.05	64.31 $\pm$ 32.51	50.06 $\pm$ 5.27
Mild preeclampsia group	46	8.67 $\pm$ 5.01*	75.28 $\pm$ 43.64*	65.97 $\pm$ 7.63*
Severe preeclampsia group	40	5.92 $\pm$ 1.97**	471.32 $\pm$ 252.67**	91.31 $\pm$ 8.24**
F		36.609	102.896	334.996
P		0.000	0.000	0.000

Note: compared with control group, *P<0.05; compared with mild preeclampsia group, **P<0.05.

2.2 三组受试者血清中血脂水平比较

三种受试者血清中 LDL-C、TG、HDL-C、TC 水平整体比较均有统计学意义 (P<0.05); 重度子痫前期组血清中 LDL-C、

2.1 三组受试者血清中 APN、TNF- α 、Apelin 水平比较

三组受试者血清中 APN、TNF- α 、Apelin 水平整体比较均有统计学意义(P<0.05); 重度子痫前期组血清中 APN 水平低于轻度子痫前期组和对照组, TNF- α 、Apelin 水平高于轻度子痫前期组和对照组(P<0.05); 轻度子痫前期组血清中 APN 水平低于对照组, TNF- α 、Apelin 水平高于对照组(P<0.05)。见表2。

TG、TC 水平高于轻度子痫前期组和对照组, HDL-C 水平低于轻度子痫前期组和对照组(P<0.05); 轻度子痫前期组 LDL-C、TC 水平高于对照组, HDL-C 水平低于对照组(P<0.05)。见表3。

表 3 三组受试者血清中血脂水平比较($\bar{x} \pm s$, mmol/L)

Table 3 Comparison of serum lipids levels of subjects in three groups ($\bar{x} \pm s$, mmol/L)

Groups	n	LDL-C	TG	HDL-C	TC
Control group	40	2.81 $\pm$ 0.53	2.28 $\pm$ 0.41	1.88 $\pm$ 0.25	4.52 $\pm$ 0.58
Mild preeclampsia group	46	3.14 $\pm$ 0.52*	2.41 $\pm$ 0.34	1.54 $\pm$ 0.19*	5.23 $\pm$ 0.54*
Severe preeclampsia group	40	3.57 $\pm$ 0.48**	2.95 $\pm$ 0.37**	1.08 $\pm$ 0.24**	5.51 $\pm$ 0.48**
F		22.266	36.710	125.811	36.578
P		0.000	0.000	0.000	0.000

Note: compared with control group, *P<0.05; compared with mild preeclampsia group, **P<0.05.

2.3 子痫前期患者血清中 APN、TNF- α 、Apelin、LDL-C、TG、HDL-C、TC 表达的相关性

Pearson 相关性分析结果显示, 子痫前期患者血清中 APN 与 TNF- α 、Apelin、LDL-C、TG 呈负相关, 与 HDL-C 呈正相关

(P<0.05), 与 TC 无相关性(P>0.05); TNF- α 与 Apelin、LDL-C、TG、TC 呈正相关, 与 HDL-C 呈负相关 (P<0.05); Apelin 与 LDL-C、TG、TC 呈正相关, 与 HDL-C 呈负相关(P<0.05)。见表4。

表 4 子痫前期患者血清中 APN、TNF- α 、Apelin、LDL-C、TG、HDL-C、TC 表达的相关性

Table 4 Correlation between serum APN, TNF- α , Apelin, LDL-C, TG, HDL-C and TC in patients with preeclampsia

Indexes	APN	TNF- α	Apelin	LDL-C	TG	HDL-C	TC
APN	-	r=-0.652 P=0.000	r=-0.673 P=0.000	r=-0.423 P=0.000	r=-0.314 P=0.026	r=0.512 P=0.000	r=-0.261 P=0.069
TNF- α	-	-	r=0.701 P=0.000	r=0.425 P=0.000	r=0.372 P=0.000	r=-0.313 P=0.027	r=0.388 P=0.002
Apelin	-	-	-	r=0.451 P=0.000	r=0.414 P=0.000	r=-0.397 P=0.000	r=0.405 P=0.000

3 讨论

妊娠期高血压疾病是妊娠期特有的一组疾病, 发病率约为 5%-12%, 子痫前期是妊娠期高血压疾病中最为常见的一种疾

病之一^[13]。目前子痫前期的具体发病机制尚无统一论,有学者^[14]提出了“两阶段”学说,第一阶段为临床前期,孕产妇的子宫螺旋动脉滋养细胞发生重铸障碍,导致胎盘缺血、缺氧,与此同时促进多种胎盘因子的释放,此阶段为子痫前期发生的病理学基础;第二阶段为胎盘因子进入血液循环,引发炎症反应、损伤内皮细胞,进而引起子痫前期的各种症状。虽然目前“两阶段”学说并未完全得到证实,但已被广泛认可,尤其是第二阶段中的炎症反应和内皮细胞损伤对子痫前期的促进作用已得到大量研究的证实^[15-17]。此外,炎症反应还可通过加重内皮细胞损伤来影响子痫前期的进展^[18]。

在本次研究中,重度子痫前期组血清中 APN 水平低于轻度子痫前期组和对照组, TNF- α 、Apelin 水平高于轻度子痫前期组和对照组 ($P<0.05$);轻度子痫前期组血清中 APN 水平低于对照组, TNF- α 、Apelin 水平高于对照组 ($P<0.05$)。这提示子痫前期患者血清中 APN 水平明显降低, TNF- α 、Apelin 水平明显升高,且三种指标的表达程度与患者的病情有关。APN 是一种由脂肪细胞分泌的蛋白质,其具有广泛的生物活性,可调节胰岛素敏感性,抑制炎症反应,改善血脂水平^[19,20]。相关研究显示^[21], APN 在子痫前期患者血清中呈低表达,与本研究结果一致,提示 APN 可抑制子痫前期的进展。TNF- α 是一种由激活的单核巨噬细胞、中性粒细胞产生的多功能因子。相关研究显示^[22], TNF- α 在子痫前期患者血清和胎盘组织中呈高表达,其可能是通过以下几个方面来影响子痫前期的疾病进展^[23-25]: (1) TNF- α 可级联放大炎症反应,对内皮细胞造成炎症损伤; (2) TNF- α 可促进血栓素的分泌,进而影响内皮细胞功能,导致内皮细胞分泌的血管舒张因子和血管收缩因子比例失衡,引起全身小动脉痉挛; (3) TNF- α 可与血管内皮细胞表面的相应受体结合,增加血浆中纤溶酶原激活抑制因子-1 的活性,进而降低纤溶性,同时促进炎症反应,共同促进血栓形成,增加血流阻力。Apelin 是血管紧张素受体相关蛋白 (APJ) 的内源性配体,在正常情况下可舒张血管,调节血压, Schreiber CA 等人^[26]的研究发现,给高血压大鼠模型静脉注射 Apelin 后可降低大鼠的舒张压和收缩压,然而给 APJ 缺乏的大鼠注射 Apelin 无法降低血压,因此可以推测 Apelin/APJ 系统对血压有重要的调节作用。然而值得注意的是,有研究显示^[27],在内皮细胞受损的情况下, Apelin 却会诱发血管平滑肌的收缩,并且可促进血管平滑肌细胞的增殖和迁移,对血压的升高起到促进的作用,这可能是 Apelin 促进子痫前期疾病进展的原因之一,然而其具体的作用机制还需进一步研究。此外, Apelin 可促进胰岛素抵抗,调节内皮细胞功能,进而影响子痫前期的进展^[28,29]。血脂异常是导致内皮细胞受损的重要原因^[30],本研究显示,重度子痫前期组血清中 LDL-C、TG、TC 水平高于轻度子痫前期组和对照组, HDL-C 水平低于轻度子痫前期组和对照组 ($P<0.05$);轻度子痫前期组 LDL-C、TC 水平高于对照组, HDL-C 水平低于对照组 ($P<0.05$),提示子痫前期患者存在明显的脂质代谢紊乱,血脂水平异常可能在疾病的发生、发展中起到一定的作用。本研究结果还显示, APN 与 TNF- α 、Apelin、LDL-C、TG 呈负相关, HDL-C 呈正相关 ($P<0.05$); TNF- α 与 Apelin、LDL-C、TG、TC 呈正相关,与 HDL-C 呈负相关 ($P<0.05$); Apelin 与 LDL-C、TG、TC 呈正相关,与 HDL-C 呈负相关 ($P<0.05$),这说明 APN、

TNF- α 、Apelin 存在一定的内在联系,且可影响血脂水平,但具体的相互作用机制还有待进一步的探讨。

综上所述,子痫前期患者血清中 APN 水平异常下降, TNF- α 、Apelin 水平异常升高,三种指标可相互影响,且可影响机体的脂质代谢水平,共同参与调节子痫前期患者的疾病进展。在后续的研究中可建立子痫前期动物模型,进一步探讨三种指标对子痫前期的具体影响机制,以为子痫前期的治疗提供新的思路。

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· 重要信息 ·

《现代生物医学进展》2019 年封面设计说明

此版封面的主体为肿瘤细胞与效应 T 细胞，并特别突出显示了肿瘤细胞表面所表达的免疫抑制受体 PD-L1。众所周知,2018 年诺贝尔生理学或医学奖授予了美国科学家詹姆斯·艾利森和日本科学家庶佑,以表彰他们所发现的抑制免疫负调节的癌症疗法——“免疫检查点疗法”，而 PD-1/PD-L1 通路正是该疗法所针对的一条十分重要的免疫抑制性信号通路。近年来,新兴的肿瘤免疫疗法蓬勃发展,PD-1/PD-L1 抑制剂作为其重要代表,一经问世就朝着靶向治疗,精准治疗的方向不断前行,为癌症治疗开创了全新的免疫治疗思路。

2019 年度杂志封面选择新型的肿瘤免疫疗法为主题,紧跟诺贝尔获奖热点,所表现内容辨识度高,符合《现代生物医学进展》的办刊主旨和特色。