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NGF 蛋白及前列腺 F2 α 受体与子宫腺肌病痛经的相关性研究 *张细庆¹ 陈文玲^{1Δ} 胡月娇¹ 万萍¹ 付婷婷¹ 唐丽娟²

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摘要 目的:研究 NGF 蛋白及前列腺 F2 α 受体(PTGFR)与子宫腺肌病痛经的相关性。**方法:**选择我院 2016 年 7 月~2017 年 7 月收治的 36 例子宫腺肌病痛经患者,按视觉模拟评分法(VAS)将痛经程度分为 11 例轻度组、14 例中度组、11 例重度组。同期选择 36 例月经正常者作为对照组。比较各组血清 NGF 蛋白和血浆 PTGFR 水平,分析二者和痛经评分之间的相关性及其单独和联合检测时诊断子宫腺肌病痛经的敏感性、特异性及受试者工作特征(ROC)曲线下面积。**结果:**子宫腺肌病痛经组血清 NGF 蛋白和血浆 PTGFR 水平均显著高于对照组($P<0.05$)。轻度痛经组血清 NGF 蛋白及血浆 PTGFR 水平均显著低于中度组和重度组($P<0.05$)。血清 NGF 蛋白和血浆 PTGFR 水平和子宫腺肌病痛经评分均呈显著正相关, r 分别为 0.812, 0.884($P<0.05$)。ROC 曲线分析结果显示血清 NGF 蛋白联合血浆 PTGFR 蛋白检测诊断子宫腺肌病痛经的 ROC 曲线下面积明显大于血清 NGF 蛋白及血浆 PTGFR 水平单独检测($P<0.05$)。**结论:**NGF 蛋白和 PTGFR 可能参与了子宫腺肌病痛经的发生和发展,二者联合检测有助于诊断子宫腺肌病痛经。血清 NGF 蛋白水平及血浆 PTGFR 蛋白水平和子宫腺肌病痛经程度呈正相关。

关键词:子宫腺肌病;痛经;神经生长因子蛋白;前列腺 F2 α 受体;相关性

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A Study on the Correlation of NGF Protein and Prostate F2 α receptor in the Adenomyosis Dysmenorrhea*ZHANG Xi-qing¹, CHEN Wen-ling^{1Δ}, HU Yue-jiao¹, WAN Ping¹, FU Ting-ting¹, TANG Li-juan²

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ABSTRACT Objective: To study the correlation of NGF protein and prostate F2 α receptor in the adenomyosis dysmenorrhea. **Methods:** 36 cases of uterine adenomyosis dysmenorrhea patients who received therapy from July 2016 to July 2016 in our hospital were treated, according to the visual analogue scale (VAS) score, those patients were divided into 11 cases in the mild groups, 14 cases in the moderate groups and 11 cases in the severe groups. In the same period, 36 patients were selected as the control group. The serum levels of NGF protein and plasma PTGFR were compared between different groups, and the correlation between them and dysmenorrhea score as well as the sensitivity, specificity and area under the ROC curve for the diagnosis of dysmenorrhea in adenomyosis when detected alone or in combination were analyzed. **Results:** The levels of serum NGF protein and plasma PTGFR in the dysmenorrhea group were significantly higher than those in the control group ($P<0.05$). The levels of serum NGF protein and plasma PTGFR in the mild dysmenorrhea group were significantly lower than those in the moderate group, and lower than the severe group ($P<0.05$). Serum levels of NGF protein and plasma PTGFR were significantly positively correlated with uterine adenomyosis dysmenorrhea scores, r were 0.812, 0.884($P<0.05$). The ROC curve analysis showed that the area under the ROC curve of serum NGF protein combined with plasma PTGFR protein in the diagnosis of adenomyosis was significantly greater than that of serum NGF protein and plasma PTGFR ($P<0.05$). **Conclusion:** NGF protein and PTGFR may be involved in the occurrence and development of dysmenorrhea in adenomyosis. Combined detection of NGF protein and PTGFR may help to diagnose the dysmenorrhea of adenomyosis. Serum levels of NGF protein and plasma PTGFR protein were positively correlated with the uterine adenomyosis.

Key words: Uterine adenomyosis; Dysmenorrhea. Nerve growth factor protein; Prostate F2 α receptor; Correlation

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前言

子宫腺肌病为子宫内膜腺体和间质侵入子宫肌层的良性

病变,以继发性加重的痛经、经期延长及经量过多为主要症状,其中痛经为患者就诊的主要诱因,多于月经开始出现并持续至整个经期,明显降低患者生活质量^[1-3]。子宫腺肌病痛经的发生机

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制尚未完全明确,深入认识其病理生理机制是有效治疗的前提。

近年来有研究报道^[5,6]腺肌病神经纤维异常分布和其盆腔疼痛有着紧密联系,神经生长因子(NGF)蛋白不仅是神经细胞调节因子,且为疼痛介质,能够于疼痛反应中发挥重要调节作用。子宫内膜为前列腺素(PG)合成的主要部位,其浓度过高能够导致子宫平滑肌收缩过度,出现痉挛性收缩,已有研究证实前列腺素^[7,8]是导致原发性痛经的重要介质,但较少关于前列腺F2 α 受体(PTGFR)的报道。本研究旨在分析 NGF 蛋白及 PTGFR 与子宫腺肌病痛经的相关性,以期于子宫腺肌病防治提供新的线索和思路。

1 资料与方法

1.1 一般资料

选择 36 例子宫腺肌病痛经患者,入选标准^[9]:伴月经过多、进行性痛经表现,妇科检查提示子宫局限性隆起、均匀性增大,且伴质硬、压痛,并经病理组织活检确诊;未合并免疫系统或者内分泌系统病变;月经规律,阴道无不规则性流血。排除标准:其他生殖器良恶性肿瘤、子宫肌瘤;围绝经期;神经系统病变。年龄 28~53 岁,平均(45.21 $\pm$ 6.30)岁;孕次 1~4 次,平均(3.01 $\pm$ 0.39)次;经期日数 5~10 天,平均(7.11 $\pm$ 0.48)天。按视觉模拟评分法(VAS)将痛经程度将其分为 11 例轻度组、14 例中度组、11 例重度组。同期选择 36 例月经正常者作为对照组,年龄 27~55

岁,平均(47.02 $\pm$ 5.11)岁;孕次 1~4 次,平均(3.45 $\pm$ 0.31)次;经期日数 4~8 天,平均(6.03 $\pm$ 0.65)天。以上各组一般资料比较差异均无统计学意义($P>0.05$),具有可比性。

1.2 检测方法

抽取各组外周肘部静脉血 2 mL,常规抗凝处理后,分离血清,将上清液标本放置于 -80 $^{\circ}$ C 低温冰箱中待检。用酶联免疫法测定血清 NGF 蛋白及血浆 PTGFR 水平。

1.3 统计学分析

数据处理选用 SPSS18.0 软件包进行统计学分析,计量资料以($\bar{x}\pm s$)表示,两组间比较选用独立样本 t 检验,多组间比较采用方差分析,计数资料以[(例)%]表示,组间比较采用 χ^2 检验,相关性分析采用 pearson 相关分析法,选用 z 检验进行受试者工作特征曲线(ROC)分析。以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 对照组和子宫腺肌病组血清 NGF 蛋白及血浆 PTGFR 水平的比较

对照组和子宫腺肌病组血清 NGF 蛋白水平分别为 (55.24 $\pm$ 6.70)和(75.11 $\pm$ 10.41)ng/L,血浆 PTGFR 水平分别为 (101.19 $\pm$ 12.77)和(362.56 $\pm$ 43.91)ng/mL,子宫腺肌病组血清 NGF 蛋白及血浆 PTGFR 水平均选择高于对照组,差异有统计学意义($P<0.05$),见图 1。

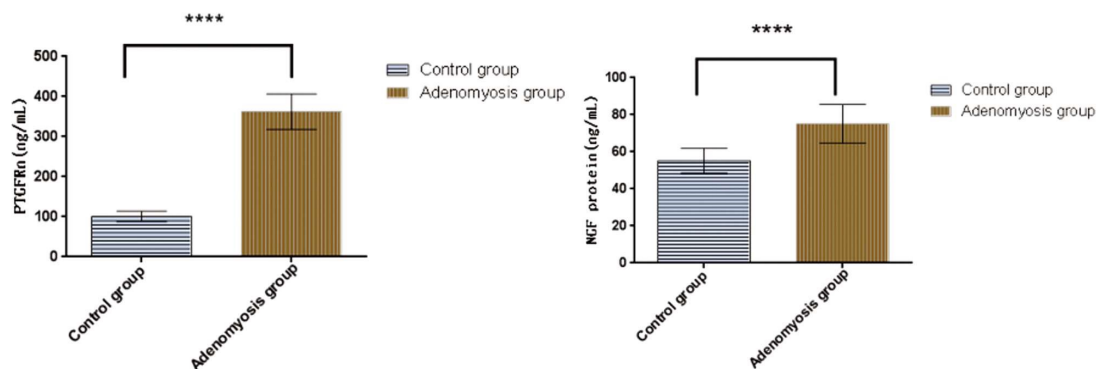


图 1 对照组和子宫腺肌病组血清 NGF 蛋白及血浆 PTGFR 水平的比较

Fig.1 Comparison of the serum NGF protein level and plasma PTGFR level between the control group and the adenomyosis group

2.2 不同痛经程度子宫腺肌病组血清 NGF 蛋白及血浆 PTGFR 水平的比较

轻度组、中度组、重度组血清 NGF 蛋白水平分别为 (60.27 $\pm$ 7.95)、(74.32 $\pm$ 9.47)、(84.29 $\pm$ 11.70)ng/L, 血浆 PTGFR

水平分别为 (189.60 $\pm$ 24.51)、(268.52 $\pm$ 35.79)、(407.51 $\pm$ 50.61) ng/mL, 轻度组血清 NGF 蛋白及血浆 PTGFR 水平明显低于中度组,中度组血清 NGF 蛋白及血浆 PTGFR 水平明显低于重度组,差异有统计学意义($P<0.05$),见图 2。

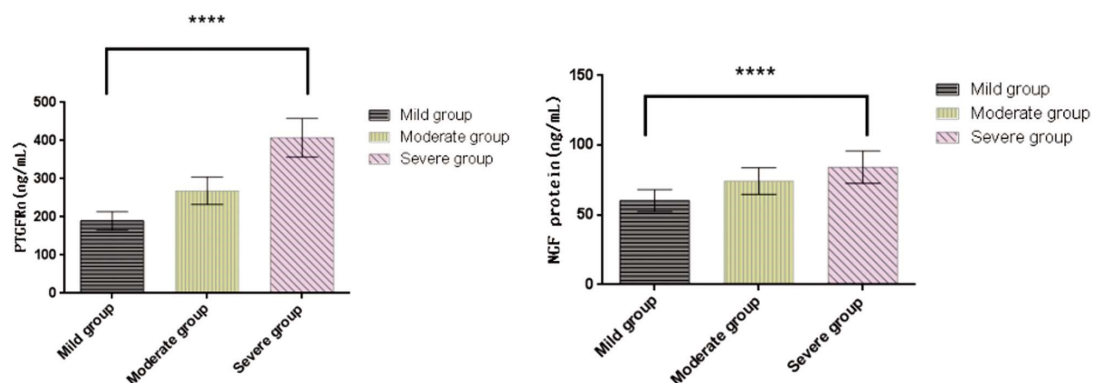


图 2 子宫腺肌病不同痛经程度组 NGF 蛋白及 PTGFR 比较

Fig.2 Comparison of NGF protein and PTGFR in different degree of dysmenorrhea in adenomyosis

2.3 子宫腺肌病患者血清 NGF 蛋白及血浆 PTGFR 水平和痛经评分的相关性分析

子宫腺肌病患者血清 NGF 蛋白和血浆 PTGFR 水平均与痛经评分均呈行政正相关, r 分别为 0.812、0.884($P < 0.05$), 见图3。

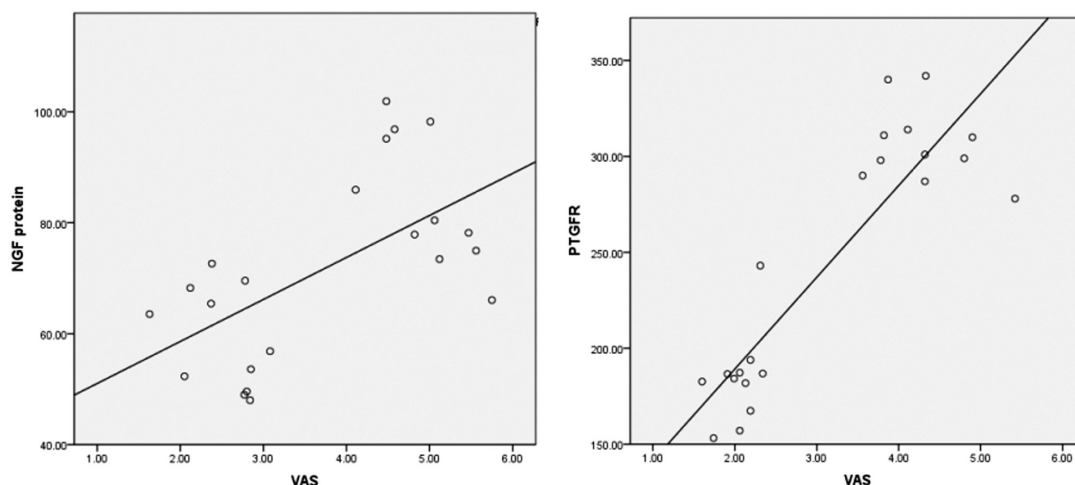


图3 子宫腺肌病患者血清 NGF 蛋白及血浆 PTGFR 水平和痛经评分的相关性

Fig.3 Correlation of the serum NGF protein and plasma PTGFR level with the dysmenorrhea score of patients with adenomyosis

2.4 血清 NGF 蛋白及血浆 PTGFR 水平诊断子宫腺肌病痛经的价值分析

血清 NGF 蛋白水平诊断子宫腺肌病痛经敏感度、特异性分别为 72.70%、90.91%, 其 ROC 曲线下面积为 0.810, 95%CI: 0.613~1.000; 血浆 PTGFR 水平诊断子宫腺肌病痛经的敏感度、特异性分别为 63.60%、90.90%, 其 ROC 曲线下面积为 0.719, 95%CI: 0.483~0.955, 血清 NGF 蛋白和血浆 PTGFR 联合诊断子宫腺肌病痛经的敏感度、特异性分别为 90.90%、81.82%, 其 ROC 曲线下面积为 0.893, 95%CI: 0.754~1.000, 联合检测诊断子宫腺肌病痛经的临床价值明显优于单一指标检测, 见图 4、表 1。

3 讨论

子宫腺肌病为妇科常见疾病, 多发于 30~50 岁经产妇, 多数患者可出现痛经症状, 表现为继发、持续性加重, 影响患者的生活质量^[10,11]。子宫腺肌病痛经的发病机制复杂, 有研究指出^[7,8]可能与神经内分泌、炎症细胞因子异常等因素有关^[12,13]。

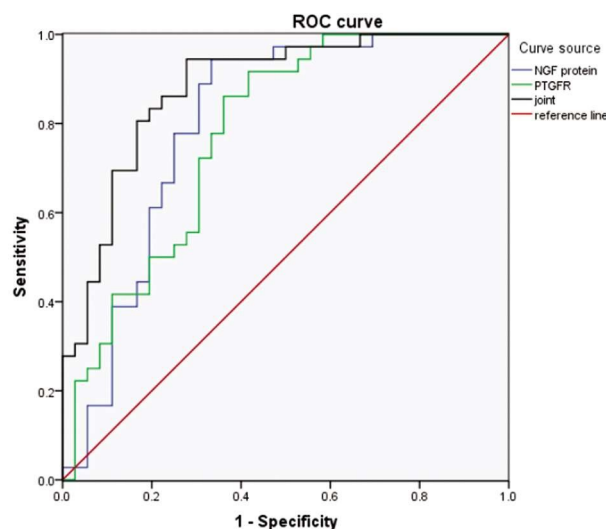


图4 血清 NGF 蛋白及血浆 PTGFR 诊断子宫腺肌病痛经的价值分析

Fig.4 Analysis of the diagnostic value of serum NGF protein and plasma PTGFR level for the dysmenorrhea in adenomyosis

表 1 血清 NGF 蛋白及血浆 PTGFR 水平诊断子宫腺肌病痛经的 ROC 曲线下面积

Table 1 The area under the horizontal curve of serum NGF protein and plasma PTGFR level

Test result variable	Area	Standard errora	Progressive sig.b	Asymptotic 95% confidence interval	
				Lower limit	Upper limit
Ngf protein	0.801	0.055	0.000	0.692	0.909
Ptgfr	0.775	0.056	0.000	0.667	0.884
Joint	0.880	0.040	0.000	0.801	0.959

NGF 属神经营养因子, 具有营养神经的作用, 可诱导交感神经纤维和感觉神经元的修复和增殖, 且可促进 T 细胞及 B 细胞增殖分化, 激活并趋化中性粒细胞、嗜酸性粒细胞, 刺激肥大细胞脱颗粒分泌 5-羟色胺、组胺等炎症因子, 引起级联反应, 刺激神经末梢, 产生致敏伤害感受器^[14,15]。同时, NGF 作为一

种疼痛物质, 能够诱导中枢疼痛传导神经微丝蛋白、降钙素基因相关肽、P 物质表达, 增加伤害感受器数目及敏感性, 从而参与并加重外周疼痛与痛觉过敏^[16,17]。相关研究显示^[18,19]NGF 于子宫内膜异位症患者病变内膜中呈高表达, 且和疼痛有着良好的相关性。动物实验研究显示^[20,21]去除转基因小鼠 NGF 基因后其

神经纤维丧失,疼痛感下降,于小鼠注射外源性 NGF 数小时后其产生温度痛觉过敏,继而发生机械性痛觉过敏。本研究结果显示子宫腺肌病痛经组血清 NGF 蛋白水平高于对照组,且痛经轻度组 NGF 蛋白水平明显低于中度组和重度组,提示血清 NGF 蛋白水平和子宫腺肌病变有关,其过度表达可能参与腺疾病痛经的发生。

PG 属不饱和脂肪酸,其生物合成和子宫其他组织类似,首选于磷脂酶 A2 作用腺癌转化至花生四烯酸,于环氧化酶诱导下转化为前列腺素 H2,再生成前列环素、PGF2 α ,发挥不同的生理活性,并于月经中起到关键生理作用^[22,23]。一方面,PGF2 α 和 PTGFR 结合后能够导致子宫平滑肌强烈收缩,引起血管挛缩,子宫缺氧、缺血,从而引起痛经,且可直接刺激作用于子宫传入神经纤维,加剧痛经^[24-26]。另一方面,炎性因子可刺激局部 PGF2 α 的产生,增加伤害性感受器敏感性,引起痛经过敏^[27,28]。又有研究报道^[29,30] PG 合成酶抑制剂能够降低局部环加氧酶活性,抑制 PG 生成,避免子宫收缩过度,缓解痛经,说明通过干预 PG 生成机制可调节痛经。本结果显示子宫腺肌病组 PTGFR 水平明显高于对照组,证实 PTGFR 能够经多种途径参与痛经,且其水平越高,痛经程度越明显,说明其可作为子宫腺肌病患者痛经程度的敏感标志物。相关性分析结果显示 NGF 蛋白和 PTGFR 水平和痛经评分呈正相关,进一步说明 NGF 蛋白和 PTGFR 水平和痛经有着良好的相关性。且经 ROC 曲线分析,我们发现血清 NGF 蛋白和血浆 PTGFR 曲线下面积均小于 NGF 蛋白和 PTGFR 联合测定组,说明联合测定联合诊断子宫腺肌病痛经的临床价值更大。

综上所述,NGF 蛋白和 PTGFR 可能参与了子宫腺肌病痛经的发生和发展,二者联合检测有助于诊断子宫腺肌病痛经。血清 NGF 蛋白水平及血浆 PTGFR 蛋白水平和子宫腺肌病痛经程度呈正相关,通过抑制其表达可能为子宫腺肌病痛经的治疗提供新的线索。

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性胆碱酯酶可以灭活蓄积的乙酰胆碱^[4]。除使用血浆置换等血液净化手段用于治疗有机磷农药中毒外,许多新药物也被用于临床治疗之中。

丙氨酰谷氨酰胺是一种常用的肠外营养剂,能够向人体提供必需氨基酸谷氨酰胺,具有保护患者胃肠道黏膜,降低其通透性减少细菌、毒素进入机体的作用^[17,18]。本研究中,我们考察了丙氨酰谷氨酰胺与血浆置换联合应用于重症有机磷中毒的疗效,结果表明与单用血浆置换相比,联合治疗能够进一步缩短患者的昏迷时间,其原因可能是联合治疗能够促进患者体内ChE的恢复。此外,联合治疗能够降低肝功能不全及消化道出血的发生率,中间综合征、肾功能不全、迟发性神经损伤的发生情况与对照组相比并无显著差异,考虑与丙氨酰谷氨酰胺发挥了对消化道黏膜的保护作用有关。已有文献报道,血浆置换后联用血液灌流等连续性血浆吸附治疗可能更有利于清除脂肪组织等释放残余毒物或新产生的炎症因子^[4,19]。本研究限于样本量有限,未进一步联用血液灌流等手段的作用,但与对于患者血清生化指标的改善作用已有研究报道基本一致。丙氨酰谷氨酰胺联合血浆置换能够明显降低观察组患者血浆AST、ALT、Cr水平,减轻毒素对肝脏的损伤,提高患者血浆Gln、Alb及TP水平,改善患者的营养状况,为患者的恢复提供了充足的营养支持^[20]。

综上所述,丙氨酰谷氨酰胺联合血浆置换能够促进重症有机磷中毒患者恢复,减少消化系统并发症发生,保护胃肠道黏膜,是一种有效的治疗方案。

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