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子宫腺肌病患者血清 NGF、PTGFR、 β -EP 水平和与痛经强度的相关性研究 *

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摘要 目的:探讨子宫腺肌病患者血清神经生长因子(NGF)、前列腺素 F2 α 受体(PTGFR)、 β -内啡肽(β -EP)水平和与痛经强度的相关性。**方法:**选择 2018 年 1 月至 2019 年 10 月我院收治的子宫腺肌病患者 80 例作为观察组,并选择同期于我院接受健康体检的 80 例无痛经、月经正常者作为对照组。比较两组一般资料、血清 NGF、PTGFR、 β -EP 水平,及观察组不同痛经强度患者血清 NGF、PTGFR、 β -EP 水平,进一步分析血清 NGF、PTGFR、 β -EP 水平和痛经强度的相关性。**结果:**两组年龄、身体质量指数(BMI)、孕次、月经周期比较差异无统计学意义($P>0.05$),观察组经期天数明显长于对照组[(7.16 $\pm$ 0.68)d vs. (5.92 $\pm$ 0.60)d]($P<0.05$);观察组血清 NGF、PTGFR 明显高于对照组, β -EP 明显低于对照组 [(78.24 $\pm$ 9.50)ng/L vs. (51.32 $\pm$ 5.18)ng/L, (370.69 $\pm$ 47.81)ng/mL vs. (95.59 $\pm$ 10.42)ng/mL, (130.87 $\pm$ 21.26)ng/L vs. (206.63 $\pm$ 31.84)ng/L]($P<0.05$);观察组患者随着痛经强度的增加,血清 NGF、PTGFR 水平逐渐升高, β -EP 水平逐渐降低($P<0.05$);Pearson 相关性分析显示血清 NGF、PTGFR 水平和 VAS 评分呈显著正相关($P<0.05$), β -EP 和 VAS 评分呈显著负相关($P<0.05$),血清 NGF 和 PTGFR 水平呈正相关($P<0.05$),血清 NGF、PTGFR 水平和 β -EP 分别呈负相关($P<0.05$)。**结论:**子宫腺肌病患者血清 NGF、PTGFR 的表达明显升高,而 β -EP 明显降低,和痛经强度之间具有密切相关。

关键词:子宫腺肌病;痛经;神经生长因子;前列腺 F2 α 受体; β -内啡肽

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Correlation of Serum Levels of NGF, PTGFR and β -EP with the Dysmenorrhea Intensity of Patients with Adenomyosis of Uterus*

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ABSTRACT Objective: To study the correlation of serum levels of nerve growth factor (NGF), prostaglandin F2 α receptor(PTGFR) and β -endorphin (β -EP) with the dysmenorrhea intensity of patients with adenomyosis of uterus. **Methods:** 80 cases with adenomyosis of uterus admitted from January 2018 to October 2019 in our hospital were selected as the observation group, and 80 cases of normal menstruation and no dysmenorrhea were selected as the control group. The general information, the serum levels of NGF, PTGFR and β -EP between two groups, and serum levels of NGF, PTGFR and β -EP between different dysmenorrhea intensity in the observation group were compared, the correlation of serum levels of NGF, PTGFR, β -EP and dysmenorrhea intensity was further analyzed. **Results:** There was no significant difference in the age, body mass index (BMI), pregnancy times and menstrual cycle between the two groups ($P>0.05$); the menstrual days in the observation group was significantly longer than those in the control group [(7.16 $\pm$ 0.68)d vs. (5.92 $\pm$ 0.60)d]($P<0.05$); the serum NGF and PTGFR in the observation group were significantly higher than those in the control group, and β -EP was significantly lower than those in the control group [(78.24 $\pm$ 9.50)ng/L vs. (51.32 $\pm$ 5.18)ng/L, (370.69 $\pm$ 47.81)ng/mL vs. (95.59 $\pm$ 10.42)ng/mL, (130.87 $\pm$ 21.26)ng/L vs. (206.63 $\pm$ 31.84)ng/L]($P<0.05$); with the increase of dysmenorrhea intensity, the serum levels of NGF, PTGFR were increased, and the levels of β -EP were decreased in the observation group($P<0.05$); the Pearson correlation analysis, there were significant positive correlation between the serum levels of NGF, PTGFR and VAS scores ($P<0.05$); there was a significant negative correlation between the β -EP and VAS score ($P<0.05$); there was a positive correlation between the serum levels of NGF and PTGFR($P<0.05$); there was a negative correlation between the serum levels of NGF, PTGFR and β -EP ($P<0.05$). **Conclusion:** The expression of serum NGF and PTGFR in patients with adenomyosis of uterus was significantly increased, it's closely related to the intensity of dysmenorrhea.

Key words: Adenomyosis of uterus; Dysmenorrhea; Nerve growth factor; Prostaglandin F2 α receptor; β -endorphin

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前言

子宫腺肌病是妇科较为常见的良性疾病,主要指子宫内膜腺体、间质侵入至子宫肌层而形成一种局部或弥漫性病变,既往该病好发于 40 岁以上的经产妇,随着近年来剖宫产、人工流产等手术的增加,其发病呈年轻化趋势^[1,2]。患者以继发性痛经、经期延长、经量过多等为主要临床表现,其中痛经是患者就诊的重要诱因。痛经在月经开始时则出现,并持续至整个经期,对患者的生活质量有着严重影响^[3,4]。目前,针对子宫腺肌病所致的痛经发病机制仍不明确,积极了解其中的病理生理机制在指导治疗中有着关键作用^[5]。

神经生长因子(NGF)作为一种神经细胞调节因子,参与着机体疼痛调节过程,可反映疼痛程度^[6]。另有研究显示前列腺素 F2 α 受体(PTGFR)在促进子宫平滑肌收缩中有着重要作用,而痛经的发生过程和子宫过度收缩之间也存在着密切联系^[7]。 β -内啡肽(β -EP)是一种具有吗啡样活性的神经多肽,具有内源性镇痛作用,也参与着生殖内分泌系统及下丘脑-垂体功能的调控过程^[8]。因此,本研究主检测了子宫腺肌病患者血清 NGF、PTGFR、 β -EP 水平,并分析三者和痛经强度的相关性,旨在为临床防治子宫腺肌病提供参考依据。

1 资料与方法

1.1 一般资料

选择 2018 年 1 月至 2019 年 10 月我院收治的子宫腺肌病患者 80 例作为观察组,纳入标准^[9]:(1)符合子宫腺肌病诊断标准,有痛经、月经不调等症状,经 B 超检查显示子宫均匀增大呈球形,子宫有触痛感,均经子宫切除术后病理组织标本证实;(2)年龄 20~55 岁,未绝经;(3)签署本研究知情同意书。排除标准^[10],

(1)合并其余生殖系统疾病,例如子宫肌瘤、子宫内膜异位症、盆腔炎症、恶性肿瘤等;(2)放置宫内节育器;(3)近 3 个月内服用过性激素类药物;(4)合并神经系统、内分泌疾病;(5)围绝经期。并选择同期于我院接受健康体检的 80 例无痛经、月经正常者作为对照组,该组患者经妇科检查均显示正常,无其余生殖系统疾病及全身性系统疾病等。

1.2 方法

收集所有受试者一般资料,包括年龄、身体质量指数(BMI)、孕次、月经周期、经期天数内容;并采集两组纳入研究后次日(观察组采集日期为子宫切除术后次日)清晨空腹静脉血 5 mL,置于 3500 min 的条件下,离心 10 min,收集上层血清液储存于零下 80℃ 的冷冻箱中待检,血清 NGF、PTGFR、 β -EP 检测所使用的酶联免疫吸附法(ELISA)均购于上品美生物工程有限公司,仪器均选择美国 BIO-RAD 公司生产的 680 型酶标仪。

观察组主诉近期 3 个月的痛经程度,并通过视觉模拟评分法(VAS)^[11]分为三组,该项评分 0~10 分,分数越高则表示疼痛感越重,判读结果,其中轻度组为 VAS 分数 ≤ 3 分为轻度组(10 例),4~6 分为中度组(54 例), ≥ 7 分为重度组(16 例)。

1.3 统计学分析

以 SPSS18.0 软件包处理,计量资料用均数 $\pm$ 标准差($\bar{x} \pm s$)表示,组间比较采用 t 检验,计数资料组间比较采用 χ^2 检验,相关性分析使用 Pearson 分析,以 $P < 0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组一般资料的比较

两组年龄、BMI、孕次、月经周期比较差异无统计学意义($P > 0.05$),观察组经期天数明显长于对照组($P < 0.05$),见表 1。

表 1 两组一般资料比较($\bar{x} \pm s$, n(%))

Table 1 Comparison of the general information between two groups($\bar{x} \pm s$, n(%))

Groups	Age(years)	BMI(kg/m ²)	Pregnancies(times)	Menstrual cycle(d)	Menstrual days(d)
Observation group(n=80)	42.04 $\pm$ 5.84	22.41 $\pm$ 2.87	2.71 $\pm$ 0.48	29.14 $\pm$ 2.50	7.16 $\pm$ 0.68*
Control group(n=80)	41.86 $\pm$ 6.21	22.50 $\pm$ 2.41	2.55 $\pm$ 0.61	28.86 $\pm$ 2.77	5.92 $\pm$ 0.60

Note: Vs. the control group, * $P < 0.05$.

2.2 两组血清 NGF、PTGFR、 β -EP 水平的比较

观察组血清 NGF、PTGFR 水平明显高于对照组,血清 β -EP

水平明显比对照组低($P < 0.05$),见表 2。

表 2 两组血清 NGF、PTGFR、 β -EP 水平的比较($\bar{x} \pm s$)

Table 2 Comparison of the serum NGF, PTGFR and β -EP levels between two groups($\bar{x} \pm s$)

Groups	NGF(ng/L)	PTGFR(ng/mL)	β -EP(ng/L)
Observation group(n=80)	78.24 $\pm$ 9.50*	370.69 $\pm$ 47.81*	130.87 $\pm$ 21.26*
Control group(n=80)	51.32 $\pm$ 5.18	95.59 $\pm$ 10.42	206.63 $\pm$ 31.84

Note: Vs the control group, * $P < 0.05$.

2.3 观察组不同痛经强度患者血清 NGF、PTGFR、 β -EP 水平的比较

根据 VAS 评分结果显示,观察组 VAS 评分范围 1~9 分,平均(5.96 $\pm$ 1.94)分,随着痛经强度的增加,血清 NGF、PTGFR

水平逐渐升高, β -EP 水平逐渐降低($P < 0.05$),见表 3。

2.4 血清 NGF、PTGFR、 β -EP 水平和 VAS 评分的相关性分析

根据 Pearson 相关性分析,血清 NGF、PTGFR 水平和 VAS 评分呈正相关($P < 0.05$),血清 β -EP 和水平 VAS 评分呈负相关

($P < 0.05$), 见表 4。

表 3 观察组不同痛经强度患者血清 NGF、PTGFR、 β -EP 比较($\bar{x} \pm s$)

Table 3 Comparison of the serum NGF, PTGFR and β -EP levels patients with different dysmenorrhea intensity in the observation group($\bar{x} \pm s$)

Groups	NGF(ng/L)	PTGFR(ng/mL)	β -EP(ng/L)
Light group(n=10)	61.33 $\pm$ 7.81	276.96 $\pm$ 25.06	171.03 $\pm$ 14.19
Moderate group(n=54)	77.18 $\pm$ 9.46*	371.18 $\pm$ 32.17*	128.44 $\pm$ 15.94*
Severe group(n=16)	92.39 $\pm$ 8.20**	427.62 $\pm$ 30.95**	113.97 $\pm$ 10.62**

Note: Vs the light group, * $P < 0.05$; vs the moderate group, ** $P < 0.05$.

表 4 血清 NGF、PTGFR、 β -EP 水平和 VAS 评分的相关性分析

Table 4 The correlative analysis of serum NGF, PTGFR, β -EP levels with VAS scores

Index	VAS score	
	r	P
NGF	0.686	< 0.05
PTGFR	0.792	< 0.05
β -EP	-0.617	< 0.05

2.5 血清 NGF、PTGFR、 β -EP 水平的相关性分析

根据 Pearson 相关性分析, 血清 NGF 和 PTGFR 水平呈显

著正相关($r = 0.837, P < 0.05$); 血清 NGF、PTGFR 水平和 β -EP 分别呈负相关($r = -0.759, -0.785, P < 0.05$), 见图 1- 图 3。

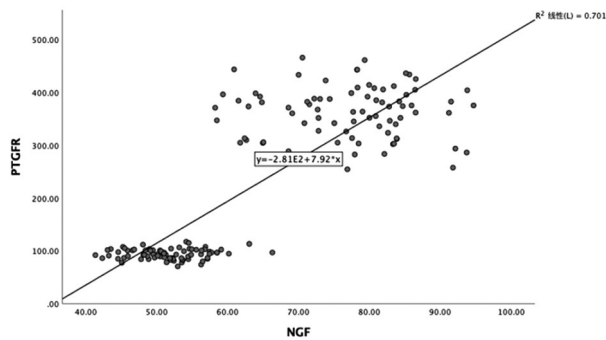


图 1 血清 NGF 和 PTGFR 的相关性散点图

Fig.1 Scatter diagram of correlation between serum NGF and PTGFR

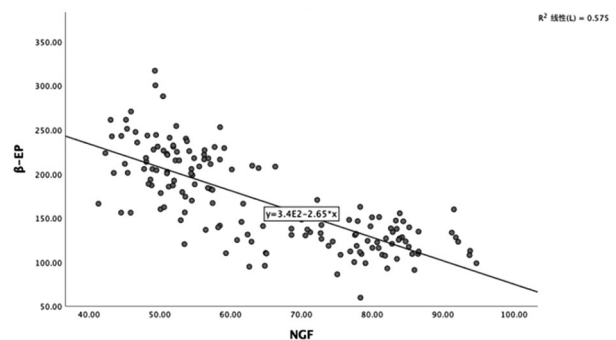


图 2 血清 NGF 和 β -EP 的相关性散点图

Fig.2 Scatter diagram of correlation between serum NGF and β -EP

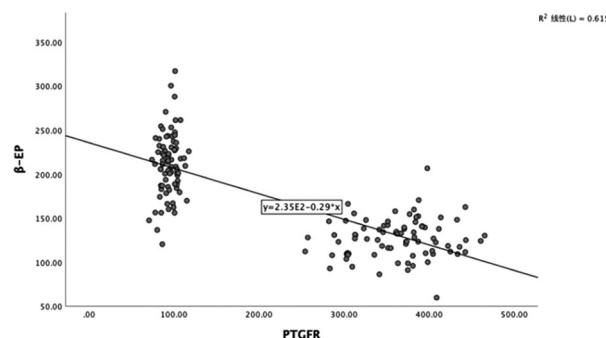


图 3 血清 PTGFR 和 β -EP 的相关性散点图

Fig.3 Scatter diagram of correlation between serum PTGFR and β -EP

3 讨论

痛经是子宫腺肌病患者常见的临床症状, 多呈继发性渐进性加重表现。子宫内膜异常和经期的异常存在着密切关系, 随着血肌层的覆盖, 可诱发肌层扩张, 促使子宫痉挛, 从而导致痛经的产生, 对女性的心理、生理均有着不同程度的影响^[12,13]。目

前, 子宫腺肌病患者出现痛经的确切机制仍不明确, 但多数研究认为其和神经内分泌紊乱、子宫平滑肌收缩、炎症反应等相关^[14,15]。

NGF 作为一种神经性营养因子, 在诱导交感神经纤维、感觉神经元的修复及增殖中发挥着重要作用, 且对 T 细胞、B 细胞的分化具有促进作用, 可激活和趋化嗜酸粒细胞、中性粒细胞、肥大细胞等, 增加 5- 羟色胺、组胺等因子的大量表达, 该过程所产生的一系列级联反应可刺激神经末梢, 产生致敏伤害感受器^[16,17]。有研究显示在子宫内膜异位症患者中, 血清 NGF 的表达明显升高, 且和疼痛之间存在着密切联系^[18]。Kwack JY 等^[19]动物实验显示敲除小鼠 NGF 基因后, 其神经纤维消失, 疼痛感减少, 而在给予外源性的 NGF 后, 小鼠出现温度痛觉过敏。本研究结果显示子宫腺肌病患者血清 NGF 的表达明显升高, 且随着痛经强度的增加表达进一步升高, 通过分析是由于 NGF 对中枢性传导神经微蛋白、P 物质的表达等具有诱导作用, 可增加伤害感受器数量和敏感性, 从而加重了外周疼痛和痛觉过敏, 且 NGF 还具有募集炎症细胞的作用, 在扩大炎症反

应的同时也将疼痛感扩大化,由此参加了子宫腺肌病患者痛经的发生和发展。

子宫内膜是前列腺素(PG)合成的重要部位,PG是一种不饱和脂肪酸,可在环氧合酶的诱导下转化成前列腺素H₂,再产生前列环素、PGF₂α等,参与着子宫肌细胞的舒张和收缩^[20,21]。目前已有较多报道证实其在浓度过高可促使子宫平滑肌过度收缩并出现痉挛,诱发痛经,且可直接对子宫传入神经纤维产生刺激作用,进一步加剧痛经^[22,23]。但对于PTGFR在子宫腺肌病痛经患者中的研究仍较少。本研究结果显示PTGFR参与着子宫腺肌病患者的痛经过程,分析可能是由于高浓度的PGF₂α对子宫平滑肌的收缩具有促进作用,可导致子宫血流量降低,高浓度的PGF₂α可刺激螺旋小动脉壁上的PTGFR的表达,促使子宫平滑肌痉挛性收缩,导致子宫腺肌病患者痛经的产生^[24,25]。

β-EP是人体中重要的神经多肽,主要来自于垂体,参与着疼痛的传递和调节过程,其可受肾上腺皮质激素释放因子(CRF)的调节,也受到肾上腺的反馈控制,产生内源性镇痛作用^[26,27]。近年来有研究发现在子宫内膜、子宫腔液中均可检测出β-EP的表达,黄体期β-EP的降低可导致子宫功能活动异常是导致痛经的关键因素^[28,29]。本研究结果显示在子宫腺肌病患者中血清β-EP的表达明显降低,且和VAS评分之间呈负相关,显示疼痛可抑制β-EP在血清中的表达。Rodriguez AR等^[30]研究也指出通过提高β-EP的表达,可更好的发挥中枢、外周镇痛效果,帮助痛经症状缓解。

本研究通过进一步分析,发现血清NGF和PTGFR呈正相关,血清NGF、PTGFR和β-EP分别呈负相关,分析可能是由于在NGF激活嗜酸粒细胞、中性粒细胞、肥大细胞等大量表达,在增加炎症级联反应的同时,会刺激局部PGF₂α的生成,增加伤害感受器的敏感性,从而进一步刺激PTGFR的大量表达,导致痛经的产生,而在疼痛感逐渐加重的过程中,会抑制β-EP的表达,导致其含量等降低,三者之间具有相辅相成的关系,共同参与了子宫腺肌病患者的痛经过程。但本研究也存在着部分不足,例如仅观察了NGF、PTGFR、β-EP在子宫腺肌病患者血清中的表达,未分析其在病灶子宫内膜及其周围组织中的表达情况,此后仍需进一步深入研究。

综上所述,子宫腺肌病患者血清NGF、PTGFR的表达明显升高,而β-EP明显降低,和痛经强度之间具有密切相关,为今后临床治疗子宫腺肌病痛经提供了一些新线索。

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(上接第 1969 页)

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