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子宫内膜异位症患者血清中 TNF- α 、LXA4、YKL-40 的表达 及其与 r-AFS 分期和痛经程度的关系 *

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摘要 目的: 探讨子宫内膜异位症 (EMs) 患者血清中肿瘤坏死因子- α (TNF- α)、免疫脂氧素 A4 (LXA4)、甲壳质酶蛋白 40 (YKL-40) 的表达及其与美国生育协会 (r-AFS) 分期和痛经程度的关系。**方法:** 选取我院于 2017 年 1 月~2018 年 1 月期间收治的 EMs 患者 92 例作为研究组。根据 r-AFS 分期将患者分为 I 期 20 例, II 期 28 例, III 期 26 例, IV 期 18 例。根据不同痛经程度将患者分为无疼痛 14 例, 轻度 24 例, 中度 32 例, 重度 22 例。另选取同期因卵巢良性囊肿、子宫腺肌瘤等行腹腔镜术治疗的患者 30 例为对照组。检测并比较两组血清 TNF- α 、LXA4、YKL-40 水平; 比较不同 r-AFS 分期和不同痛经程度患者血清 TNF- α 、LXA4、YKL-40 水平; 采用 Pearson 相关性分析方法分析血清 TNF- α 、LXA4、YKL-40 水平与 r-AFS 分期和痛经程度的相关性。**结果:** 研究组患者 TNF- α 、YKL-40 水平均显著高于对照组, 而 LXA4 水平显著低于对照组 ($P<0.05$)。随着 r-AFS 分期的升高, EMs 患者血清 TNF- α 、YKL-40 水平逐渐升高, LXA4 水平逐渐降低 ($P<0.05$)。随着痛经程度的增加, EMs 患者血清 TNF- α 、YKL-40 水平逐渐升高, LXA4 水平逐渐降低 ($P<0.05$)。Pearson 相关性分析显示, EMs 患者 TNF- α 、YKL-40 水平与 r-AFS 分期和痛经程度呈正相关, LXA4 与 r-AFS 分期和痛经程度呈负相关 ($P<0.05$)。**结论:** EMs 患者中血清 TNF- α 、YKL-40 水平呈高表达, LXA4 呈低表达。上述指标与 EMs 患者 r-AFS 分期和痛经程度关系密切, 可考虑将其作为临床诊断 EMs 的生物学指标。

关键词: 子宫内膜异位症; 肿瘤坏死因子- α ; 免疫脂氧素 A4; 甲壳质酶蛋白 40; r-AFS 分期; 痛经程度; 相关性

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Expression of TNF- α , LXA4 and YKL-40 in Serum of Patients with Endometriosis and Its Relationship with r-AFS Stage and Dysmenorrhea*

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ABSTRACT Objective: To investigate the expression of tumor necrosis factor- α (TNF- α), immuno-lipoxygenin A4 (LXA4) and chitinase protein 40 (YKL-40) in patients with endometriosis (EMs) and its relationship to the stage of American Fertility Association (r-AFS) and the degree of dysmenorrhea. **Methods:** 92 patients with EMs who were admitted to our hospital from January 2017 to January 2018 were selected as the study group. According to r-AFS, the patients were divided into I stage with 20 cases, II stage with 28 cases, III stage with 26 cases, IV stage with 18 cases. According to the degree of dysmenorrhea, the patients were divided into no pain with 14 cases, light with 24 cases, moderate with 32 cases and severe with 22 cases. Another 30 patients who underwent laparoscopic surgery for uterine adenomyoma and ovarian benign cyst were selected as control group. The serum levels of TNF- α , LXA4 and YKL-40 were detected and compared between the two groups. The serum levels of TNF- α , LXA4 and YKL-40 in patients with different r-AFS staging and different dysmenorrhea were compared. The correlation between serum TNF- α , LXA4, YKL-40 level and r-AFS staging and dysmenorrhea score was analyzed by Pearson correlation analysis. **Results:** The levels of TNF- α and YKL-40 in the study group were significantly higher than those in the control group, while the LXA4 level was significantly lower in the study group than that in the control group ($P<0.05$). With the increase of r-AFS stage, serum TNF- α and YKL-40 levels in EMs patients gradually increased, and LXA4 levels gradually decreased ($P<0.05$). With the increase of the scores of different dysmenorrhea, the levels of TNF- α and YKL-40 in EMs patients gradually increased, while LXA4 levels gradually decreased ($P<0.05$). TNF- α and YKL-40 levels in EMs patients were positively correlated with r-AFS stage and dysmenorrhea score. LXA4 was negatively correlated with r-AFS stage and dysmenorrhea score. **Conclusion:** The serum levels of TNF- α and YKL-40 were highly expressed in EMs patients and LXA4 was low. These indicators are closely related to the r-AFS stage and dysmenorrhea in EMs patients, and they can be considered as biological indicators for clinical diagnosis of EMs.

Key words: Endometriosis; Tumor necrosis factor- α ; Immune lipoxin A4; Chitinase protein 40; r-AFS stage; Dysmenorrhea; Correlation

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前言

子宫内膜异位症(Endometriosis, EMs)是指有活性的内膜细胞种植在子宫内膜以外的位置而形成的一种常见的女性妇科疾病,病变可波及所有的盆腔组织以及气管,临床通常表现为痛经、月经异常、不孕以及慢性盆腔疼痛等症状^[1-3]。虽然 EMs 为良性疾病,且治疗方式多样,但治疗后易复发,疗效一般,给患者生活质量造成严重影响,因此早期的诊断和治疗是降低 EMs 发生、发展的关键^[4,5]。腹腔镜为 EMs 的诊断金标准,然而该诊断方式为有创诊断,加之价格昂贵,重复使用率低,故寻找更多的 EMs 诊断指标已成为临床医师的研究热点。有学者认为炎症因子在 EMs 的发生、发展中起到重要作用,肿瘤坏死因子- α (Tumor necrosis factor- α , TNF- α)是常见的炎性介质,可通过激活巨噬细胞以及小胶质细胞产生炎症反应^[6]。免疫脂氧素 A4(Immuno lipoxigenin A4, LXA4)对多种炎性介质、炎性细胞起到负调节作用^[7]。甲壳质酶蛋白 40 (Chitinase protein 40, YKL-40)是哺乳动物壳质酶蛋白家族中的成员之一,已有研究^[8]显示在 EMs 患者组织中 YKL-40 表达水平高于健康子宫内膜组织,但其具体联系还需进一步确认。鉴于此,本研究通过探讨 EMs 患者血清中 TNF- α 、LXA4、YKL-40 的表达及其与美国生育协会(American Fertility Society, r-AFS)分期和痛经程度的关系,旨在为 EMs 病情评估提供参考。

1 资料与方法

1.1 一般资料

选取我院于 2017 年 1 月~2018 年 1 月期间收治的 EMs 患者 92 例作为研究组。纳入标准:(1)所有患者均符合《妇产科学》中有关 EMs 的相关诊断标准^[9];(2)经腹腔镜病理活检确诊为 EMs;(3)均未接受过激素或者避孕药等治疗;(4)入院前 6 个月未接受过放化疗治疗;(5)所有患者知情本研究并签署知情同意书。排除标准:(1)合并恶性肿瘤者;(2)伴有严重心、肝、肾等脏器功能障碍者;(3)合并高血压、糖尿病、心脏病等慢性疾病者;(4)妊娠或哺乳期妇女;(5)合并有肝炎、结核等感染性

疾病者。患者年龄 25~44 岁,平均(32.48 $\pm$ 5.49)岁;病程 4~13 年,平均(8.19 $\pm$ 1.45)年;月经周期 27~33d,平均(30.14 $\pm$ 1.31) d;孕次 1~3 次,平均(2.04 $\pm$ 0.18)次;疾病类型:腹膜型 31 例,卵巢型 28 例,阴道直肠隔型 33 例。r-AFS 分期:I 期 20 例,II 期 28 例,III 期 26 例,IV 期 18 例。另选取 30 例同期因子宫肌瘤、卵巢良性囊肿等行腹腔镜手术治疗的患者为对照组,年龄 24~46 岁,平均(33.18 $\pm$ 4.57)岁,病程 5~12 年,平均(9.23 $\pm$ 1.36)年;月经周期 28~35d,平均(30.61 $\pm$ 1.25)d;孕次 1~3 次,平均(2.18 $\pm$ 0.46)次。两组患者年龄、病程、月经周期以及孕次等一般资料比较统计学无差异($P>0.05$),提示组间可比,本研究经我院伦理委员会批准同意。

1.2 方法

1.2.1 标本采集与检测 采集所有受试者清晨空腹静脉血 6 mL,3000 r/min 离心 8 min,取上清液置于 -20℃冰箱中待测。采用酶联免疫吸附试验检测受试者血清 TNF- α 、YKL-40、LXA4 水平,试剂盒购自深圳晶美生物科技有限公司。

1.2.2 痛经程度评定标准 采用视觉疼痛模拟(Visual pain analogue scale, VAS)评分^[10]评价患者疼痛程度,无需服药记为 0 分;需服药,但对日常生活无影响记为 1~3 分;服药后缓解,对日常生活有影响记为 4~6 分;服药后仍不能缓解记为 7~10 分。其中无疼痛(0 分)14 例,轻度(1~3 分)24 例,中度(4~6 分)32 例,重度(7~10 分)22 例。

1.3 统计学方法

数据分析采用 SPSS 23.0 统计学软件。计量资料以均值 $\pm$ 标准差表示,多组数据应用单因素 F 分析,两组数据应用 t 检验,计数资料以%表示,实施 χ^2 检验,采用 Pearson 相关性分析方法分析血清 TNF- α 、LXA4、YKL-40 水平与 r-AFS 分期和痛经程度的相关性,检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 研究组与对照组血清 TNF- α 、LXA4、YKL-40 水平比较

研究组患者 TNF- α 、YKL-40 水平均显著高于对照组,而 LXA4 水平显著低于对照组($P<0.05$),详见表 1。

表 1 研究组与对照组血清 TNF- α 、LXA4、YKL-40 水平比较($\bar{x} \pm s$)

Table 1 Comparison of serum TNF- α , LXA4 and YKL-40 levels between the study group and the control group($\bar{x} \pm s$)

Groups	n	TNF- α (ng/mL)	LXA4(ng/L)	YKL-40(ng/L)
Control group	30	0.87 $\pm$ 0.27	589.03 $\pm$ 25.49	36.28 $\pm$ 2.21
Study group	92	1.58 $\pm$ 0.46	286.37 $\pm$ 20.78	89.07 $\pm$ 3.45
t	-	8.002	65.402	78.594
P	-	0.000	0.000	0.000

2.2 研究组不同 r-AFS 分期患者血清 TNF- α 、LXA4、YKL-40 水平比较

研究组不同 r-AFS 分期患者血清 TNF- α 、LXA4、YKL-40 水平比较差异有统计学意义($P<0.05$);随着 r-AFS 分期的升高,EMs 患者血清 TNF- α 、YKL-40 水平逐渐升高,LXA4 水平逐渐降低($P<0.05$),详见表 2。

2.3 研究组不同痛经程度患者血清 TNF- α 、LXA4、YKL-40 水平比较

研究组不同痛经程度患者血清 TNF- α 、LXA4、YKL-40 水平比较差异有统计学意义($P<0.05$);随着痛经程度的增加,EMs 患者血清 TNF- α 、YKL-40 水平逐渐升高,LXA4 水平逐渐降低($P<0.05$),详见表 3。

2.4 血清 TNF- α 、LXA4、YKL-40 水平与 r-AFS 分期和痛经程度的相关性

Pearson 相关性分析显示,EMs 患者 TNF- α 、YKL-40 水平与 r-AFS 分期和痛经程度呈正相关,LXA4 与 r-AFS 分期和痛

经程度呈负相关($P<0.05$),详见表 4。

表 2 研究组不同 r-AFS 分期患者血清 TNF- α 、LXA4、YKL-40 水平比较($\bar{x} \pm s$)

Table 2 Comparison of serum levels of TNF- α , LXA4 and YKL-40 in different r-AFS stages of study group($\bar{x} \pm s$)

r-AFS stages	n	TNF- α (ng/mL)	LXA4(ng/L)	YKL-40(ng/L)
Istage	20	0.87 $\pm$ 0.46	459.14 $\pm$ 21.37	63.54 $\pm$ 5.19
IIstage	28	1.45 $\pm$ 0.42*	343.51 $\pm$ 31.46*	77.68 $\pm$ 6.22*
IIIstage	26	1.98 $\pm$ 0.38*#	236.69 $\pm$ 19.53*#	92.85 $\pm$ 6.31*#
IVstage	18	2.58 $\pm$ 0.29*#&	144.05 $\pm$ 16.08*#&	119.76 $\pm$ 5.21*#&
F	-	3.573	13.378	7.259
P	-	0.016	0.000	0.000

Note: compared with I stage, * $P<0.05$; compared with II stage, # $P<0.05$; compared with III stage, & $P<0.05$.

表 3 研究组不同痛经程度患者血清 TNF- α 、LXA4、YKL-40 水平比较($\bar{x} \pm s$)

Table 3 Comparison of serum levels of TNF- α , LXA4 and YKL-40 in different groups of patients with dysmenorrhea($\bar{x} \pm s$)

Degree of dysmenorrhea	n	TNF- α (ng/mL)	LXA4(ng/L)	YKL-40(ng/L)
No pain	14	0.81 $\pm$ 0.33	452.72 $\pm$ 32.65	68.83 $\pm$ 6.17
Light	24	1.47 $\pm$ 0.35*	329.16 $\pm$ 26.44*	81.16 $\pm$ 5.05*
Moderate	32	1.88 $\pm$ 0.42*#	219.72 $\pm$ 20.95*#	95.83 $\pm$ 6.17*#
Severe	22	2.47 $\pm$ 0.25*#&	149.16 $\pm$ 19.84*#&	116.16 $\pm$ 7.95*#&
F	-	3.072	12.618	7.082
P	-	0.021	0.000	0.000

Note: compared with no pain, * $P<0.05$; compared with moderate, # $P<0.05$; compared with severe, & $P<0.05$.

表 4 血清 TNF- α 、LXA4、YKL-40 水平与 r-AFS 分期和痛经程度的相关性

Table 4 Correlation between serum levels of TNF- α , LXA4, YKL-40 and r-AFS stage and dysmenorrhea

Indexes	r-AFS stage		Degree of dysmenorrhea	
	r	P	r	P
TNF- α	0.301	0.012	0.324	0.011
LXA4	-0.432	0.001	-0.312	0.006
YKL-40	0.373	0.009	0.481	0.008

3 讨论

近年来 EMs 发病率不断上升,育龄女性中约有 5%~15% 患有 EMs^[11,12]。由于该病治疗较为棘手,无论是药物保守治疗或是手术治疗,均难以彻底治愈,且复发率较高,对患者日常生活带来严重影响^[13]。腹腔镜虽然可以较全面的观察病变,然而近年来有不少学者对腹腔镜的可靠性、确切性提出了质疑,比如镜检无法观察到隐匿或腹膜下器官内组织病变、镜检的阴性或阳性并不能明确判断是否患有 EMs^[14,15]。EMs 发病机制复杂,临床关于 EMs 的发病机制也有多种学说,相关研究认为,EMs 是一种与炎症相关的疾病,也有学者认为 EMs 是一种致病因素较为复杂的多基因遗传性疾病^[16-18]。既往有研究证明^[19,20],EMs 的发生可分为细胞增生、分化以及侵入三个过程,上述过程往往依赖于细胞粘附分子活动,因此,EMs 的发生可能与细胞、基质之间的相互作用失调有关。本研究通过观察 EMs 患者和正常在位内膜志愿者中的血清 TNF- α 、LXA4、YKL-40 水平,

评价上述指标在 EMs 患者的诊疗意义。

TNF- α 属于血管活性因子之一,具有促进细胞分化生长、调控免疫应答等多种生物学功能,在炎症反应以及神经病相关性慢性疼痛等发生过程中均有参与^[21]。Sipak-Szmigiel O 等人^[22]研究发现 TNF- α 可促进间皮细胞和异位内膜间形成粘连,促进基底新生血管的产生,同时还具有活化细胞外基质的作用,最终致使异位内膜组织与周围组织粘连从而形成 EMs,其在 EMs 的发生、发展过程中发挥重要作用。LXA4 是一种内源性炎症消退介质,通过与 ALXR 受体结合而发挥强效的促炎症消退效应,具有协调急性炎症转化为慢性炎症的作用^[23]。LXA4 的产生依赖于 5-脂氧化酶,通过阻断 5-脂氧化酶可以减少 LXA4 的合成,正常情况下,体内炎症因子可促进 5-脂氧化酶的表达和活性,且 LXA4 的表达与体内炎症因子处于动态平衡,若体内存在过度的炎症反应时,炎症因子抑制 5-脂氧化酶的表达和活性,降低 LXA4 的表达,导致炎症-促炎症这一动态平衡被打破,导致 EMs 的发生^[24]。故 LXA4 可成为早期检测

EMs 的生物学指标之一。YKL-40 的生物学特性目前尚不十分明确,然而有相关体外实验表明,YKL-40 具有促进细胞生长、迁移以及入侵等功能^[25]。且已有多项报道显示 YKL-40 在多种炎性细胞、肿瘤细胞中均过度表达和分泌^[26-28]。YKL-40 参与了 EMs 的慢性炎症发生、发展过程,其主要作用机制可能是与刺激内皮细胞迁移以及调节血管内皮细胞形成新的分枝小血管有关^[29,30]。本次研究结果表明,研究组患者 TNF- α 、YKL-40 水平均显著高于对照组,而 LXA4 水平显著低于对照组。且随着 EMs 患者病情的恶化,TNF- α 、YKL-40 在 EMs 患者体内呈现高表达,LXA4 呈现低表达,可见上述三种指标均可作为临床检测 EMs 的生物学报指标。通过相关性分析显示 EMs 患者 TNF- α 、YKL-40 水平与 r-AFS 分期和痛经程度呈正相关,LXA4 与 r-AFS 分期和痛经程度呈负相关。提示在 EMs 病情发展过程中,TNF- α 、YKL-40、LXA4 均发挥着重要作用,可能通过不同的作用机制参与疾病的发生、发展。

综上所述,血清 TNF- α 、YKL-40、LXA4 水平可反映 EMs 患者病情严重程度以及痛经状态,可作为临床检测 EMs 新的补充检测手段,对 EMs 患者的诊断、病情评估以及预后具有一定的临床应用价值。

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列环素的合成与释放。此外,治疗期间两组患者的不良反应发生率分别为 4.76%、16.67%,提示联合治疗并未增加患者的不良反应,安全性高。

综上所述,本研究结果表明疏血通联合依那普利治疗老年慢性心力衰竭的临床效果显著优于单用依那普利治疗,可能与其显著降低患者的血清 N 末端钠尿肽前体水平,改善患者的心功能和血液流变学的各项指标有关。

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