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神经细胞黏附因子在子宫腺肌病病灶中的表达及意义 *

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摘要 目的：探究神经细胞黏附因子(NCAM)在子宫腺肌病病灶中的表达及意义。**方法：**将 2016 年 6 月 ~2017 年 6 月在我院接受治疗的 80 例子宫腺肌病患者作为研究对象，包括分泌期与增生期各 40 例，采用免疫组化法检测，其在位内膜、异位内膜组织中 NCAM 表达情况，并以同期我院 40 例正常者子宫内膜标本作为对照。对子宫腺肌病患者痛经程度给予 NRS 疼痛评估，比较其 NCAM 的表达。**结果：**80 例子宫腺肌病在位内膜、异位内膜均存在 NCAM 表达，40 例正常内膜腺上皮有 38 例存在 NCAM 表达，2 例正常内膜无表达。NCAM 在异位内膜组织中的表达明显高于在位内膜及正常子宫内膜(P<0.05)，差异均有统计学意义。NCAM 在在位内膜组织分泌期表达与增生期差异有统计学意义(P<0.05)；子宫腺肌病异位病灶 NCAM 表达与患者 NRS 评分呈现明显正相关(r=0.824，P<0.05)。**结论：**NCAM 在异位子宫内膜高表达，可能参与了子宫内膜异位症的发生和发展，并与患者痛经程度呈现出正相关。

关键词：神经细胞黏附因子；子宫腺肌病；异位内膜；表达；免疫组化

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Expression and Significance of Nerve Cell Adhesion Factor in Adenomyosis Lesions*

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ABSTRACT Objective: To explore the expression and significance of nerve cell adhesion factor (NCAM) in adenomyosis. **Methods:** From June 2016 to June 2016 in our hospital for treatment of 80 cases of uterine adenomyosis patients as the research object, including the secretory and hyperplasia of the 40 patients, using immunohistochemical method to detect, its in ectopic, NCAM expression in ectopic endometrium tissue, and with the same period from 40 cases of normal endometrium specimens in comparison. NRS pain assessment was performed in patients with adenomyosis, and the expression of NCAM was compared. **Results:** in 80 cases of adenomyosis, there were NCAM expression in the endometrium and endometrium, and in 40 cases of normal endometrium, there were 38 cases of NCAM expression, and 2 cases of normal endometrium were not expressed. The expression of NCAM was significantly higher than that in the endometrium and normal endometrium (P<0.05), and the difference was statistically significant. There were statistically significant differences between the secretion period and the hyperplasia of NCAM (P<0.05). The NCAM expression of adenomyosis was positively correlated with NRS score (r=0.824, P<0.05). **Conclusion:** NCAM may be involved in the occurrence and development of endometriosis, and is positively correlated with the degree of dysmenorrhea.

Key words: Nerve cell adhesion factor; Adenomyosis of the uterus; Endometrium; Express; Immunohistochemical

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前言

子宫腺肌病是临床上一种极为常见的妇科疾病，多发生于育龄期女性群体[1,2]，一般在经期前 1 周开始出现下腹正中剧烈疼痛，经期结束后才有所缓解，严重影响着患者的生活质量。研究表明 NCAM 在免疫细胞及神经细胞均有不同程度表达，且大多数神经组织、内分泌组织中发现有 NCAM 存在[3]。有学者在大鼠实验中发现 NCAM 在大鼠子宫内膜异位灶中有表达，并提出 NCAM 可能与子宫内膜异位灶痛经相关[4]。本研究选取 80 例在我院接受治疗的子宫腺肌病患者为研究对象，探讨了 NCAM 在子宫腺肌病病灶中的表达及意义，结果报道如下：

1 资料与方法

1.1 一般资料

选择 2016 年 6 月 ~2017 年 6 月在我院接受治疗的子宫腺肌病患者 80 例。年龄为 30~49 岁，平均年龄为(42.4± 4.3)岁。

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采集其在位内膜与异位病灶组织标本，分泌期与增生期均为40例，根据NRS疼痛评分对患者痛经程度给予评估，见表1。将同期在我院行子宫切除术的40例子宫肌瘤患者正常子宫肌瘤组织作为对照组，年龄为31~48岁，平均年龄为(42.3± 4.2)岁。纳入标准：(1)诊断结果与国际子宫腺肌病临床诊断标准相符[5]；(2)入组患者均对研究知情、同意，自愿参与研究，并签署知情同意书；(3)术前6个月未接受过激素治疗。排除标准：(1)存在重要脏器疾病者及伴随心、肝、肾功能疾病者；(2)意识模糊及精神紊乱者；(3)合并严重器质性病变者；(4)临床资料不全者[6,7]。两组患者一般人口学资料比较比较采用均无统计学意义(P>0.05)，具有可比性。该研究得到医学伦理会的认可，并征得了临床科室的支持。

表1 80例子宫腺肌病患者痛经程度NRS分级

Table 1 NRS classification of 80 cases of adenomyosis patients with dysmenorrhea

The degree of dysmenorrhea	n	Percentage
Mild pain	10	12.5%
Moderate pain	12	15.0%
Severe pain	58	72.5%
Total	80	100.0%

1.2 免疫组化检测

对所有收集的标本给予常规甲醛固定，经过一系列脱水、石蜡包埋等相关处理后，实施切片、烤片，所需时间为1 h。采用脱蜡剂、梯度乙醇等进行脱蜡处理，在蒸馏水中浸泡，反复3次，5 min/ 次，加入3%H_2O_2，阻断过氧化物酶。修复切片，放置于高压锅中修复，加热时间为2 min，常规室温下冷，然后将山羊封闭血清滴入，调整相应的温度进行为期30 min孵育，加入1∶100特异性鼠抗人NCAM抗体进行为期4 h孵育，过夜，PBS冲洗，再次孵育30 min，PBS冲洗后在其中加入过氧化物酶标记链霉素工作液，实施显色处理。选取病理学证实的NCAM阳性肺癌切片为对照。

1.3 痛经评分标准

痛经评分采用NRS疼痛评分，为0~10分，0~3分表示轻度疼痛，4~6分表示中度疼痛，7~10分表示重度疼痛[8,9]。

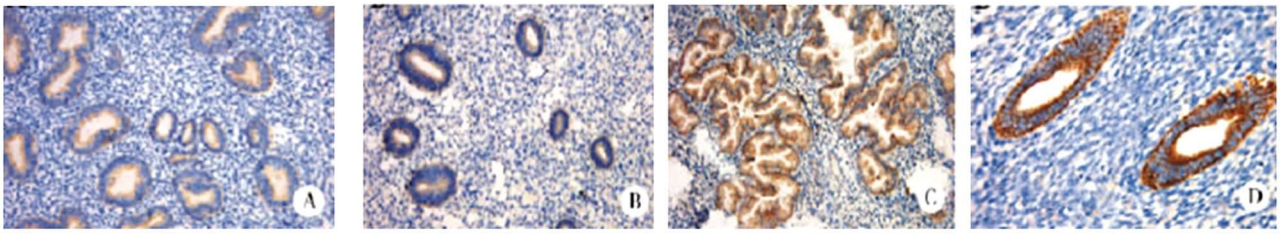
1.4 统计学方法

数据采用统计学软件SPPSS18.0处理，所有的计数资料均用%表示，进行x^2检验，计量资料选择标准差($\bar{x}$± s)表示，采取t检验，以P<0.05表示为差异有统计学意义。

2 结果

2.1 三组NCAM表达的比较

NCAM在所有患者在位内膜、异位内膜均可见表达，40例正常内膜腺上皮有38例存在NCAM表达，2例正常内膜无表达。NCAM在异位内膜组织中的表达明显高于在位内膜及正常对照组(P<0.05)，差异有统计学意义；NCAM在在位内膜组织分泌期表达与增生期差异有统计学意义(P<0.05)。见图1、表2。



A 对照组　B 在位内膜增生期　C 在位内膜分泌期　D 异位内膜组织

A 对照组　B 在位内膜增生期　C 在位内膜分泌期　D异位内膜组织

A control group　B during endometrial hyperplasia　C during endometrial secretion　D heterotopic tissue.

图1 子宫内膜腺上皮组织中NCAM的表达情况

Fig.1 Expression of NCAM in endometrial adenoepithelial tissue

2.2 子宫腺肌病异位内膜NCAM的表达与痛经程度的关系

子宫腺肌病异位内膜NCAM表达与患者NRS评分呈现出明显的正相关(r=0.824，P<0.05)，见图1。

3 讨论

子宫腺肌病是雌激素依赖性疾病，其病因机制复杂，目前研究已证实其发生与雌激素分泌异常有着密不可分的联系[10-15]。子宫腺肌病多发生于30-50岁的经产妇，约15%合并有子宫内膜异位症，约50%合并有子宫肌瘤。子宫腺肌症主要表现症状为痛经和不孕[11]。作为一种糖蛋白，NCAM黏附在细胞与细胞外基质或介导细胞与细胞间，参与细胞信号传导，且在神经细胞及内分泌细胞中也有一定的分布，与嗜异性或嗜同性细胞结合能够可有效调节细胞内外各项生理活动，营造良好的神经生长微环境[16-18]。

本研究中，NCAM在异位子宫内膜腺上皮表达水平显著高于对照组，其与在位内膜增生期NCAM表达差异无统计学意义，提示当子宫内膜与基层交界位置受损时，NCAM在子宫内膜腺上皮组织与肌层组织黏附参与介导[19-22]。相关文献报道

表 2 三组 NCAM 表达情况分析($\bar{x}\pm$ s)

Table 2 Analysis of three groups of NCAM expressions($\bar{x}\pm$ s)

Group	n	H-score
Control group	40	2.15± 0.93*
Secretory period	14	2.25± 0.97
Hyperplasia period	26	2.08± 0.96
Endometrial tissue	80	2.27± 0.55*
Secretory period	40	2.46± 0.58
Hyperplasia period	40	2.07± 0.44^
Heterotopic tissue	80	3.12± 0.82
Secretory period	40	3.18± 0.74
Hyperplasia period	40	3.05± 0.88

Note: *P<0.01, compared with ectopic endometrium compared with in ectopic secretory ^P<0.05.

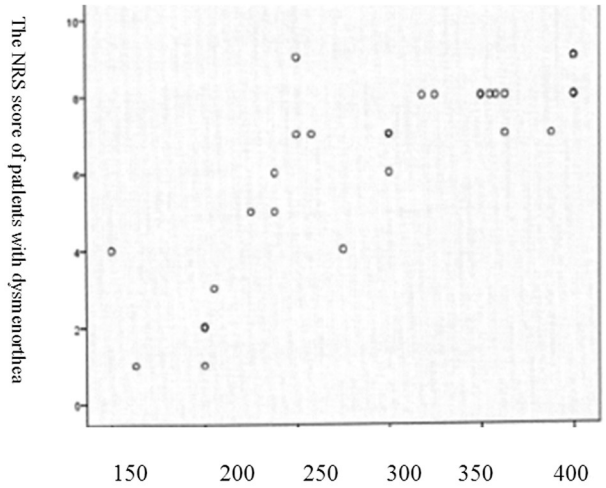


图 2 子宫腺肌病异位病灶 NCAM 表达与 NRS 评分的关系

Fig.2 The relationship between NCAM expression in uterine adenomyosis and NRS score

月经周期与 NCAM 在子宫腺肌病在位内膜中的表达有着密不可分的联系[23-26]。与增生期相比,NCAM 在分泌期表达明显较高，但异位内膜组织 NCAM 分泌期表达与增生期则无明显差异。其主要与两个因素有关:(1)NCAM 在异位病灶呈现高表达;(2)正常机体内膜激素受体呈现低表达。有学者在研究发现雌激素、孕激素受体均在子宫腺肌病病灶中有一定的参与作用，在雌二醇作用下，猕猴神经元中 NCAM 会受到相应的刺激,此时给予孕酮则能够对该刺激起到一定的拮抗作用[27,28]。因此,雌孕激素对 NCAM 表达具有调节作用,进而呈现出周期性变化。NCAM 在子宫腺肌病异位病灶中的表达与患者痛经呈现出明显正相关,患者 NCAM 表达越强,患者疼痛越严重。当异位病灶腺上皮 NCAM 处于高表达状态，其将会对病灶周围神经生长起到促进作用,造成痛觉传入冲动,引起痛经[29,30]。

综上所述,NCAM 在异位子宫内膜高表达，可能参与了子宫内膜异位症的发生和发展,并与患者痛经程度呈现出正相关。

参考文献(References)

[1] 蒋雪梅,曹宁宁,徐丽雅,等.E-cadherin、VEGF、MMP-9 在子宫腺肌病和腹壁子宫内膜异位症病变组织中的表达及意义 [J]. 海南医学, 2017, 28(20): 3300-3302
Jiang Xue-mei, Cao Ning-ning, Xu Li-ya, et al. Expression and significance of e-cadherin, VEGF, mmp-9 in uterine adenomyosis and endometriosis of the abdominal wall [J]. Hainan medicine, 2017, 28 (20): 33-3302

[2] 贾晨阳,汪沙,李金皎.细胞黏附因子在子宫腺肌病发病机制中作用的研究进展[J].现代妇产科进展, 2017, 26(7): 545-547
Jia Chen-yang, Wang Sha, Li Jin-jiao. Research progress on the role of cell adhesion factors in the pathogenesis of adenomyosis [J]. Progress of modern obstetrics and gynecology, 2017, 26(7): 545-547

[3] 郭静,陈丽,罗宁,等.TLR4 信号介导内膜间质细胞侵袭增殖促子宫腺肌症发病的研究[J].现代妇产科进展, 2015, 12(9): 672-676
Guo Jing, Chen Li, Luo Ning, et al. Studies on the pathogenesis of adenomyosis induced by TLR4 signaling mediated interstitial cell invasion[J]. Progress of modern obstetrics and gynecology, 2015, 12(9): 672-676

[4] 余星,陈雄,黄娟.子宫内膜异位性疾病患者子宫内膜组织 EGFR 和 EMT 相关蛋白表达及意义[J].山东医药, 2015, 24(44): 18-20
Yu Xing, Chen Xiong, Huang Juan. Expression and significance of EGFR and EMT related proteins in endometriosis of endometriosis patients [J]. Shandong medicine, 2015, 24(44): 18-20

[5] Khan K N, Kitajima M, Hiraki K, et al. Decreased expression of human heat shock protein 70 in the endometria and pathological lesions of women with adenomyosis and uterine myoma after GnRH agonist therapy[J]. European Journal of Obstetrics & Gynecology, 2015, 187: 6-13

[6] 陈丽,李彩霞,郭静,等.子宫动脉阻断后腺肌病在位及病灶内膜组织凋亡现象观察[J].现代妇产科进展, 2016, 25(4): 261-264
Chen Li, Li Cai-xia, Guo Jing, et al. Observation of apoptosis of endometriosis after uterine artery occlusion [J]. Modern gynecology and obstetrics, 2016, 25(4): 261-264

[7] 程凤杰,刘欣,张晓燕,等.Survivin、Livin 和 VEGF 在子宫腺肌病异位内膜组织中的表达及意义[J].山东医药, 2015, 12(13): 52-53
Cheng Feng-jie, Liu Xin, Zhang Xiao-yan, et al. Expression and significance of Survivin, Livin and VEGF in endometriosis of adenomyosis [J]. Shandong medicine, 2015, 12(13): 52-53

[8] 李雁,叶瑶,徐步芳,等.抗神经生长因子抗体用于改善子宫腺肌病小鼠宫腔内环境的研究[J].生殖与避孕, 2015, 35(6): 353-358
Li Yan, Ye Yao, Xu Gao-fang, et al. Anti-neurogrowth factor antibody was used to improve the study of uterine environment of uterine adenomyosis mice [J]. Reproductive and contraception, 2015, 35(6): 353-358

[9] 蒋建发,肖松舒,薛敏.子宫腺肌病在位内膜差异基因表达及信号转导网络构建[J].现代妇产科进展, 2017, 26(6): 409-412
Jiang Jian-fa, Xiao Song-shu, Xue Min. Construction of the gene expression and signal transduction network in the endometriosis of adenomyosis of uterus[J]. Progress of modern obstetrics and gynecology, 2017, 26(6): 409-412

[10] 张子杰.子宫腺肌病病灶 NGF 蛋白表达水平及神经纤维植入密度与患者痛经的关系研究[J].中国妇幼保健, 2015, 30(19): 3132-3134
Zhang Zi-jie. Study on the relationship between NGF protein expression level and nerve fiber implantation density in patients with adenomyosis of the uterus [J]. Chinese maternal and child health, 2015, 30 (19): 3132-3134

[11] 蒋静,陈燕,吴宏. GRIM-19 在子宫腺肌病中的表达及促进疾病发展的机制研究[J].重庆医学, 2017, 46(27): 3811-3815
Jiang Jing, Chen Yan, Wu Hong. Research on the mechanism of expression and promotion of disease development in uterine adenomyosis [J]. Chongqing medicine, 2017, 46(27): 3811-3815

[12] 余冬青,黄晓彤,孙静,等.消症方含药血清对腺肌病子宫内膜间质细胞迁移、侵袭及黏附能力的影响 [J]. 广东医学, 2015, 12(11): 1642-1645
Yu Dong-qing, Huang Xiao-tong, Sun Jing, et al. Effects of serum containing drug serum on the migration, invasion and adhesion ability of endometrial stromal cells of adenomyosis[J]. Guangdong medicine, 2015, 12(11): 1642-1645

[13] 李彦博, 李新, 谭爰丽,等.神经生长因子的分布情况与子宫内膜异位症疼痛的相关性研究[J].实用临床医药杂志, 2015, 19(17): 45-47
Li Yan-bo, Li Xin, Tan Yuan-li, et al. The distribution of nerve growth factor and the correlation of endometriosis pain research [J]. Journal of clinical medicine, 2015, 19(17): 45-47

[14] 贾晨阳,段华,汪沙,等.子宫腺肌病 EMI 区 VEGF 与 b-FGF 的表达及其与 MVD 的相关性分析 [J]. 中国计划生育和妇产科, 2017, 9 (4): 60-64
Jia Chen-yang, Duan Hua, Wang Sha, et al. Expression of VEGF and b-fgf in EMI region of uterine adenomyosis and its correlation with MVD[J]. China family planning and gynecology, 2017, 9(4): 60-64

[15] Zhou S, Yi T, Liu R, et al. Proteomics identification of annexin A2 as a key mediator in the metastasis and proangiogenesis of endometrial cells in human adenomyosis [J]. Molecular & Cellular Proteomics Mcp, 2012, 11(7): 3929-3936

[16] Choi Y J, Chang J A, Kim Y A, et al. Innervation in women with uterine myoma and adenomyosis [J]. Obstet Gynecol Sci, 2015, 58(2): 150-156

[17] Choi Y J, Chang J A, Kim Y A, et al. Innervation in women with uterine myoma and adenomyosis [M]. Environmental Software Systems. Frameworks of eEnvironment. Springer Berlin Heidelberg, 2015: 558-565

[18] Zhang H, Wang Z, Jin H. Expression and significance of microvessel density in lesions of adenomyosis [J]. Journal of Modern Oncology, 2013

[19] Zhang Z J, Pathology D O. Relationship between adenomyosis lesion NGF protein levels and nerve fiber density in patients with implanted dysmenorrhea[J]. Maternal & Child Health Care of China, 2015

[20] Lin-Na X U, Zhang S F, Wei-Guo H U, et al. The expression of NGF in serum and local lesion with adenomyosis dysmenorrhea[J]. Chinese Journal of Practical Gynecology & Obstetrics, 2014, 30(1): 59-63

[21] Arellano M L B D, Arnold J, Lang H, et al. Evidence of neurotrophic events due to peritoneal endometriotic lesions [J]. Cytokine, 2013, 62 (2): 253-261

[22] Kolioulis I, Zafrakas M, Grimbizis G, et al. Immunohistochemical expression pattern of metastasis suppressor KISS-1 protein in adenomyosis lesions and normal endometrium[J]. European Journal of Obstetrics & Gynecology & Reproductive Biology, 2017, 210: 64-68

[23] Khan K N, Kitajima M, Hiraki K, et al. Decreased expression of human heat shock protein 70 in the endometria and pathological lesions of women with adenomyosis and uterine myoma after GnRH agonist therapy[J]. European Journal of Obstetrics & Gynecology, 2015, 187: 6-13

[24] Jiang Z, Xu W, Gang D, et al. P53 and Murine Double Mimute 2 (MDM2) Expression Changes and Significance in Different Types of Endometrial Lesions[J].Medical Science Monitor International Medical Journal of Experimental & Clinical Research, 2016, 22: 4786-4793

[25] Zeng Y, Guan Y, Kunyin L I. Role of estrogen,estrogen receptors, and aromatase in the pathogenesis of uterine adenomyosis [J]. Journal of Southern Medical University, 2017, 37(3): 383

[26] Drăghici I M, Drăghici L, Cojocaru M, et al. The immunoprofile of interstitial Cajal cells within adenomyosis/endometriosis lesions [J]. Rom J Morphol Embryol, 2015, 56(1): 133-138

[27] An M, Li D, Yuan M, et al. Interaction of macrophages and endometrial cells induces epithelial-mesenchymal transition-like processes in adenomyosis?[J]. Biology of Reproduction, 2017, 96(1): 46-57

[28] Wang F, Shi X, Qin X, et al. Expression of CD56 in patients with adenomyosis and its correlation with dysmenorrhea [J]. European Journal of Obstetrics & Gynecology, 2015, 194(21): 174-175

[29] Wang J, Deng X, Yang Y, et al. Expression of GRIM-19 in adenomyosis and its possible role in pathogenesis [J]. Fertility & Sterility, 2016, 105(4): 1093-1101

[30] Zhang H, Liu J, Zhao X, et al. Loss of PP2A and PTEN immunoexpression coexists with survivin overexpression in adenomyosis[J]. Reproductive Biology, 2014, 14(3): 200-205