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不同亚型食管癌反流病患者胃组织白细胞介素-1 β 表达差异及临床意义*林玲,冉亚梅,郎秀琼,何雨芬,陈强,纪雷,杨敏 Δ

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摘要:目的 对比研究典型症状与非典型症状的非糜烂反流病(NERD)患者胃组织白细胞介素-1 β (IL-1 β)的差异及临床意义。方法 NERD 患者 70 例,按照有无典型反流症状,分为 2 个亚型:典型症状组 43 例、非典型症状组 27 例;采用化学发光法评估不同亚型 NERD 患者胃组织中 IL-1 β 的表达差异。结果 与非典型症状组比较,典型症状组 IL-1 β 水平明显降低,差异有统计学意义[(75.26 \pm 7.20) pg/mL vs. (107.22 \pm 13.13) pg/mL, $P=0.039$]。结论 典型症状和非典型症状的 NERD 患者胃组织 IL-1 β 有明显差异,提示 IL-1 β 可能参与了不同亚型的 NERD 发生的机制。

关键词:胃食管反流;白细胞介素-1 β ;烧心;反酸;食管外症状

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The expression of interleukin 1 β in the patients with typical symptoms and atypical symptoms of NERD*Lin ling, Ran Yamei, Lang Xiuqiong, He Yuqin, Chen Qiang, Ji Lei, Yang Min Δ

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Abstract: Objective To study the differences and its clinical significance of the expression of interleukin 1-beta (interleukin 1 beta, IL-1 beta) between the patients with typical symptoms and atypical symptoms of non-erosive reflux diseases(NERD) in the stomach tissue. Methods 70 cases of patients with NERD were divided into two subtypes according to the presence or absence of typical reflux symptoms, the typical group (43 cases), and the atypical symptoms group (27 cases); The interleukin-1 assay kit (chemiluminescence) was applied to assess the differences of IL-1 β in stomach tissue of NERD patients with different subtypes. Results Compared with the atypical symptoms group, the concentration of IL-1 beta in typical symptoms group was obviously lower and the difference was statistically significant [(75.26 \pm 7.20) pg/mL vs. (107.22 \pm 13.13) pg/mL, $P=0.039$]. Conclusion Significant differences of the expression of IL-1 β in the stomach tissue were found between the typical symptoms group and the atypical symptoms group, suggesting that IL-1 β may be involved in the occurrence of different subtypes of NERD.

Key words: gastroesophageal reflux; interleukin-1 β ; heart burn; acid reflux; extra-esophageal symptoms

非糜烂性反流病(non-erosive reflux disease, NERD)是指存在反流相关的不适症状,但内镜下未见食管黏膜损害的疾病,是临床上最常见的胃食管反流病(gastroesophageal reflux disease, GERD),约占 GERD 的 50%~70%。按照有无典型反流症状,可分为 2 个亚型:典型症状 NERD、非典型症状 NERD,后者主要表现为反复咳嗽、咽部不适、异物感、咽痛、胸闷、声嘶、哮喘、胸痛及失眠等食管外症状^[1-2]。不同亚型的 NERD 发病机制多样而复杂,存在何种差异至今尚未完全阐明,对抗酸治疗总体效果不佳。近年来,有学者提出 NERD 在食管黏膜出现微观改变之前,已有炎症存在的现象,并提出细胞因子可能介导食管上皮免疫炎症^[3]。目前已发现多种趋化因子、细胞因子参与了食管的黏膜炎症^[4-6]。白细胞介素-1 β (IL-1 β)是具有多种功能的炎症因子,近年来诸多研究^[7-8]表明,IL-1 β 及 IL-1 受体拮抗剂(IL-1RN)基因多态性的改变与 GERD 发生相关。有研究发现,炎症因子 IL-1 β 和 IL-1 受体(interleukin-1 receptor, IL-1R)在胃酸的分泌过程中起着重要的作用,可调节胃黏膜上皮功能,抑制胃酸分泌,且其与 IL-1 β 多态性基因降低胃食管反流病发病风险有关^[9]。IL-1 β 是免疫炎症反应中最关键的功能细胞因子,参与了免疫反应的细胞增殖、分化并提高其功能^[4]。有关 IL-1 β 在有典型症状、非典型症状 NERD 患者中的作用研究鲜见文献报道。为此,本文

对比研究典型症状与非典型症状的 NERD 患者胃组织的 IL-1 β 的差异,旨在阐明 IL-1 β 在不同亚型的 NERD 发病机制中的作用。

1 资料与方法

1.1 一般资料 选取 2014 年 3~7 月在本院就诊的 70 例 NERD 患者,男 20 例,女 50 例,性别比 1.0:2.5;年龄 21~64 岁,平均 42.70 岁。典型症状组 43 例,占 61.43%(43/70),男 11 例,女 32 例,性别比 1.0:2.9,年龄 21~64 岁,平均 43.65 岁;非典型症状组 27 例,占 38.57%(27/70),男 9 例,女 18 例,性别比 1.0:2.0,年龄 27~55 岁,平均 41.19 岁。入选标准,(1)典型症状 NERD 组:最近 3 月内有烧心、反酸、胸骨后疼痛、返食等典型症状,反流性疾病问卷 RDQ 量表评分大于 12 分;(2)非典型症状 NERD 组:存在有非典型的胃食管反流症状,主要表现为消化道外症状(如反复咳嗽、咽部不适、异物感、咽痛、胸闷、哮喘、瘰疬症、声音嘶哑、非心源性胸痛及失眠等),亦可伴有上消化道不适(包括上腹痛、腹胀、嗝气、上腹不适、恶心、呕吐等)^[1-2];(3)内镜阴性,即食管下无黏膜破损;(4)近 4 周内未服用 PPI 和(或)H2 受体拮抗剂类药物;(5)既往无消化系统病史,无消化道手术史,无可引起胃食管反流症状的全身性疾病。排除标准:年龄小于 18 岁,Barrett 食管,食管良性肿瘤患者,食管静脉曲张者,严重食管动力障碍性疾病,严重

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胃疾患(息肉、癌),曾行胃及食管手术者,糖尿病患者,酗酒者及凝血机制障碍者。本研究经第三军医大学大坪医院伦理委员会批准,所有参加者均知情同意。由 Pearson 相关性分析得出年龄与 IL-1 β 无明显相关性。经 χ^2 检验得两组性别构成统计学差异无统计学意义($P>0.05$)。

1.2 方法

1.2.1 内镜检查及组织标本的采集 所有患者均禁食禁饮 8 h 以上,使用奥林巴斯(Olympus)电子胃镜检查。在内镜直视下,所有患者均钳取距离幽门 2~3 cm 的胃窦部组织标本 2~3 块,置于洁净 EP 管中,于 -70 $^{\circ}\text{C}$ 低温冰箱中保存备用。解冻标本后取 30 mg 组织溶于 10 mL 的磷酸盐缓冲液中,于冰上研磨成浆^[10]。1 000 \times g 离心 10 min,取上清液,并立即送检验科测定。

1.2.2 胃组织 IL-1 β 的检测 采用 IL-1 β 检测试剂盒[西门子医学诊断产品(上海)有限公司]行化学发光法(采用 IMMULITE 1000 化学发光分析仪)测定胃黏膜组织中 IL-1 β 水平。

1.3 统计学处理 采用 SPSS18.0 软件进行数据分析,计量资料以 $\bar{x}\pm s$ 表示,采用独立样本的 t 检验,计数资料采用率或构成比以百分比(%)表示,计数资料采用 χ^2 检验,以 $P<0.05$ 为差异有统计学意义。

2 结 果

与非典型症状组比较,典型症状组 IL-1 β 水平明显降低,差异有统计学意义[(75.26 \pm 7.20) pg/mL vs. (107.22 \pm 13.13) pg/mL, $P=0.039$]。

3 讨 论

本文表明,不同亚型的 NERD 患者,即典型症状和非典型症状的 NERD 患者胃组织 IL-1 β 水平差异有统计学意义($P<0.05$),且典型组的 IL-1 β 水平比非典型组低,由此提示 IL-1 β 可能参与了不同亚型 NERD 炎症介导发病机制的过程。

NERD 是 GERD 的最常见类型。但是由于缺乏内镜下的改变,目前 NERD 的诊断主要基于症状及证实这些症状与反流相关的证据。IL-1 β 是免疫炎症反应中最关键的功能细胞因子,参与了免疫反应的细胞增殖、分化。有研究^[11-14]发现,IL-1 β 在胃酸的分泌中起着重要的作用,既可调节胃黏膜上皮壁细胞的功能,抑制上皮壁细胞分泌胃酸;又因其多态性基因可降低 GERD 风险。Fitzgerald 等^[15]发现 GERD 患者食管黏膜内 IL-1 β mRNA 表达水平较正常黏膜及 Barrett 食管黏膜明显增加;而 Ando 等^[9]研究表明,IL-1 β 基因型与 GERD 之间存在密切联系,即遗传因素在 GERD 的发病中也起着重要作用。有研究发现编码这两个蛋白的基因 IL-1 β 基因和 IL-1RN 的多态性可能与 GERD 内镜下炎症程度有关^[16]。另有研究^[9]发现,IL-1 β -511 * TT 基因型及 T 等位基因是 RE 发病危险因素,同时有文献报道 IL-1RN * 2 等位基因是 GERD 的保护因素^[16]。

据有关文献^[10]报道健康组胃组织中的 IL-1 β 水平较 NERD 组高,且差异有统计学意义($P<0.05$)。Kandulski 等^[17]研究发现糜烂性食管炎、NERD 患者贲门食管黏膜 IL-1 β 表达较健康组明显增加。本研究表明,非典型症状 NERD 患者胃黏膜 IL-1 β 水平较比典型症状组明显增高,推测其机制可能为:IL-1 β * TT 基因及 T 等位基因可能导致非典型 NERD 患者胃黏膜 IL-1 β 水平相对较高,同时 IL-1 β 可以诱发胃黏膜的炎症反应,一方面使腺体萎缩,向萎缩性胃炎发展^[13-14,16,18];另一方面可能使壁细胞大量破坏,即通过直接或

间接作用共同减少胃酸分泌,从而降低非典型症状的 NERD 患者烧心、反酸等症状的发生,而以食管外症状(如咳嗽、咽部不适、异物感、咽痛、胸闷、哮喘)或伴有上消化道不适等为主要表现^[9,14]。但其确切的机制尚有待进一步研究。

总之,本研究结果表明 IL-1 β 参与了不同亚型 NERD 发生的病理生理机制。尽管质子泵抑制剂对酸相关反流性食管炎黏膜损伤的疗效已被广为接受,然而对非典型症状的 NERD 患者复杂症状的缓解并不尽如人意。NERD 炎症介导发病机制的提出,为不同亚型 NERD 的治疗带来了新的视角。从 IL-1 β 等炎症因子及其调控机制入手,并关注 IL-1 β 与其他导致 NERD 发生病因之间的相互作用,可能是部分 NERD 患者治疗的新方向。

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