

doi: 10.13241/j.cnki.pmb.2020.09.024

过敏性鼻炎患者血清 IL-8、IL-22 及 TNF- α 水平的变化 及其与病情严重程度关系的研究*

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摘要 目的:探究过敏性鼻炎患者血清白介素-8(IL-8)、白介素-22(IL-22)及肿瘤坏死因子- α (TNF- α)水平的变化及其与病情严重程度的关系。**方法:**选择2018年2月至2019年6月期间我院诊治的99例过敏性鼻炎患者作为鼻炎组,选择同期进行健康体检的99例健康志愿者作为健康组。采用酶联免疫吸附法检测血清IL-8、IL-22及TNF- α 水平,按照世界卫生组织对过敏性鼻炎的分度标准将鼻炎组进一步分为轻度组、中度组和重度组,比较不同病情严重程度患者过敏性鼻炎评分量表(SFAR)评分、视觉模拟量表(VAS)评分以及血清IL-8、IL-22及TNF- α 水平,采用Pearson相关性分析血清IL-8、IL-22及TNF- α 水平与SFAR评分和VAS评分的相关性。**结果:**与健康组相比,鼻炎组的血清IL-8、IL-22及TNF- α 水平均明显升高($P<0.05$)。与轻度组相比,中度组和重度组的SFAR评分、VAS评分以及血清IL-8、IL-22及TNF- α 水平明显升高,且中度组明显高于轻度组($P<0.05$)。血清IL-8、IL-22及TNF- α 水平与SFAR评分和VAS评分均呈正相关($P<0.05$)。**结论:**血清IL-8、IL-22及TNF- α 水平升高与过敏性鼻炎的发生密切相关,并且随患者病情加剧而上调。同时,血清IL-8、IL-22及TNF- α 水平与SFAR评分和VAS评分均呈正相关性,在临床诊断过敏性鼻炎的严重程度上具有一定应用价值。

关键词:过敏性鼻炎;白介素-8;白介素-22;肿瘤坏死因子- α ;过敏性鼻炎评分量表;视觉模拟量表评分

中图分类号:R765.21 **文献标识码:**A **文章编号:**1673-6273(2020)09-1716-04

Changes in Serum IL-8, IL-22 and TNF- α Levels in Patients with Allergic Rhinitis and Their Relationship with Severity of the Disease*

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ABSTRACT Objective: To investigate the relationship between serum IL-8, IL-22 and TNF- α levels and severity of allergic rhinitis.

Methods: 99 cases of allergic rhinitis diagnosed and treated in our hospital from February 2018 to June 2019 were selected as the rhinitis group, and 99 cases of healthy personnel who underwent physical examination during the same period were selected as the healthy group. Enzyme-linked immunosorbent method was used to test two groups of serum IL-8, IL-22 and TNF- α level. According to the world health organization on allergic rhinitis of dividing standards, rhinitis group further divided into mild, moderate and severe groups, Score of allergic rhinitis scale (SFAR), Visual analogue scale (VAS) score and the serum levels of IL 8, IL-22 and TNF- α level were compared among three groups, the Pearson correlation between serum IL-8, IL-22, TNF- α level and SFAR score and VAS score were analyzed.

Results: Compared with the healthy group, the serum levels of IL-8, IL-22 and TNF- α in the rhinitis group were significantly higher ($P<0.05$). Compared with the mild group, the SFAR score, VAS score, serum IL-8, IL-22 and TNF- α levels in the moderate group and the severe group were significantly higher than those in the mild group ($P<0.05$). Serum levels of IL-8, IL-22 and TNF- α were positively correlated with SFAR and VAS ($P<0.05$). **Conclusion:** The elevation of serum IL-8, IL-22 and TNF- α levels was closely related to the occurrence of allergic rhinitis and was up-regulated with the aggravation of the disease. At the same time, serum IL-8, IL-22 and TNF- α levels were positively correlated with SFAR score and VAS score, which had certain application value in clinical diagnosis of the severity of allergic rhinitis.

Key words: Allergic rhinitis; Interleukin-8; InterleukinS-22; Tumor necrosis factor- α ; Score For Allergic Rhinitis

Chinese Library Classification(CLC): R765.21 **Document code:** A

Article ID: 1673-6273(2020)09-1716-04

* 基金项目:北京市科学技术委员会科研计划项目(D151100006322019)

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(收稿日期:2020-01-10 接受日期:2020-01-31)

前言

过敏性鼻炎是耳鼻喉科较为常见的疾病类型之一,发病率在 30%左右,并且近年来呈逐年增长趋势^[1]。过敏性鼻炎会导致患者出现鼻塞、连续性喷嚏和鼻痒等症状,对患者的日常生活影响较大,严重时会导致患者的嗅觉功能障碍^[2]。目前学界对过敏性鼻炎的发病机制仍然缺乏了解,已有研究报道显示免疫功能异常活化和炎症反应的发生是导致过敏性鼻炎的主要病因^[3]。白介素-8(interleukin-8, IL-8)是由单核-巨噬细胞分泌的趋化因子,通过作用于中性粒细胞发挥免疫和炎症调节功能^[4],与支气管管和急性呼吸衰竭等炎症性疾病的发生发展密切相关,并且可以作为急性呼吸衰竭患者的预后诊断指标^[5,6]。白介素-22(interleukin-22, IL-22)主要由 T 淋巴细胞和自然杀伤性细胞分泌产生,其受体蛋白在肝脏、肺和肾脏等组织器官中普遍表达,参与炎症反应的发生^[7],在哮喘和结核性胸膜炎等呼吸系统炎症性疾病的发病过程中发挥重要作用^[8,9]。肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)是由巨噬细胞分泌产生的一种系统性炎症细胞因子,通过作用于淋巴细胞和粒细胞等免疫细胞发挥免疫调节功能,在炎症反应的发生发展过程中也起到重要作用^[10],在肺炎和慢性阻塞性肺疾病等呼吸系统疾病发病过程中起到一定促进作用^[11,12]。本研究通过检测血清 IL-8、IL-22 及 TNF- α 水平,旨在探讨其在过敏性鼻炎患者中的水平及其与过敏性鼻炎病情严重程度的关系。现报道结果如下。

1 资料与方法

1.1 一般资料

选择 2018 年 2 月至 2019 年 6 月期间我院诊治的 99 例过敏性鼻炎患者作为研究对象,并将其纳入鼻炎组。纳入标准:(1)符合过敏性鼻炎的临床诊断标准^[13]:具有每次打喷嚏次数在 3 次以上、鼻塞、鼻痒和流清涕等临床症状,鼻分泌物镜检结果显示嗜酸性粒细胞占比 >5%。(2)病程在 1 年以上;(3)临床资料完整;(4)所有研究对象知情同意,且签署知情同意书。排除标准:(1)入组前 2 个月内进行过激素治疗者;(2)合并其它过敏性疾病者;(3)存在肝肾功能障碍者;(4)存在全身感染性疾病者;(5)存在自身免疫性疾病者。鼻炎组患者年龄 21-69 岁,平均(41.89 $\pm$ 8.75)岁。男性 59 名,女性 40 名。病程 1.1-12.5 年,平均(6.74 $\pm$ 3.61)年。选择同期在我院进行健康体检的 99 名健康志愿者作为健康组,其中男性 53 名,女性 46 名。年龄 20-73 岁,平均(43.67 $\pm$ 7.93)岁。鼻炎组和健康组在年龄和性别比例等一般资料上比较无统计学差异($P>0.05$),具有可比性。我院伦理委员会已批准本研究。

1.2 方法

所有患者于入院次日采集清晨空腹静脉血 3 mL,健康体检者于体检当日采集清晨空腹静脉血 3 mL,室温下 5000 r/min 离心 15 min,离心半径 12.5 cm,吸取上清液置于 -20℃ 冰箱中用于后续检测。血清 IL-8、IL-22 及 TNF- α 水平检测均采用酶联免疫吸附法,分别采用 IL-8 检测试剂盒(上海晶抗生物工程有限公司,货号:EA00953,规格:96T)、IL-22 检测试剂盒(上海抚生实业有限公司,货号:E1996,规格:96T)及 TNF- α 检测试剂盒(上海乔羽生物科技有限公司,货号:MB10200,规格:96T)对血清 IL-8、IL-22 及 TNF- α 水平进行检测,实验操作严格按照试剂盒说明书进行。按照世界卫生组织对过敏性鼻炎的分级标准^[14],将过敏性鼻炎分为轻度 8 例、中度 16 例和重度 75 例。评估项目包括:(1)日常学习和工作;(2)日常娱乐、体育和社交活动;(3)睡眠。以上三项均没有受到影响则为轻度,三项中有一项受影响则为中度,两项及以上受影响则为重度。

1.3 观察指标

比较健康组和鼻炎组及不同病情严重程度过敏性鼻炎患者血清 IL-8、IL-22 及 TNF- α 水平,比较不同病情严重程度患者过敏性鼻炎评分量表(Score For Allergic Rhinitis, SFAR)和视觉模拟量表(Visual Analog Scales, VAS)评分,其中 SFAR 评分项目包括鼻痒、流清涕、鼻塞和连续性喷嚏四项,每项评分为 0-3 分,总评分为四项评分之和,最高为 12 分,评分越高表示患者病情越严重^[15]。VAS 评分采用 VAS 卡尺进行评估,VAS 卡尺为两面,其中一面显示 0-10 分,其中 0 分为无症状,而 10 分为症状严重。另一面的两端则标识有痛苦和微笑两种表情。将表情一面呈递给患者,并让患者对自身病情和临床症状的严重性进行评估,患者根据自评结果调整卡尺上游标位置,医师则记录下另一面对应的数值^[16]。采用 spearman 相关性分析血清 IL-8、IL-22 及 TNF- α 水平与 SFAR 评分和 VAS 评分的相关性。

1.4 统计学分析

采用 SPSS20.0 统计学软件对临床数据进行分析。平均年龄、血清 IL-8、IL-22 及 TNF- α 水平等计量资料采用平均值 $\pm$ 标准差的方式表示,采用独立样本 t 检验。采用 F 检验对不同病情严重程度患者进行多组间比较。计数资料以率表示,采用 χ^2 检验。血清 IL-8、IL-22 及 TNF- α 水平与 SFAR 评分和 VAS 评分的相关性采用 Pearson 相关性分析, $P<0.05$ 则表示差异具有统计学意义。

2 结果

2.1 鼻炎组和健康组血清 IL-8、IL-22 及 TNF- α 水平比较

鼻炎组血清 IL-8、IL-22 及 TNF- α 水平明显高于健康组($P<0.05$)。统计结果见表 1。

表 1 鼻炎组和健康组血清 IL-8、IL-22 及 TNF- α 水平比较($\bar{x}\pm s$)

Table 1 Comparison of serum IL-8, IL-22 and TNF- α levels between the rhinitis group and the healthy group($\bar{x}\pm s$)

Groups	n	IL-8(ng/L)	IL-22(ng/L)	TNF- α (ng/L)
Healthy group	99	2.75 $\pm$ 0.54	1.74 $\pm$ 0.34	2.08 $\pm$ 0.41
Rhinitis group	99	20.73 $\pm$ 3.70	12.89 $\pm$ 2.30	14.81 $\pm$ 2.64
t		47.823	47.677	47.334
P		0.000	0.000	0.000

2.2 不同病情严重程度过敏性鼻炎患者 SFAR 评分、VAS 评分以及炎症因子水平比较

不同病情严重程度过敏性鼻炎患者 SFAR 评分、VAS 评分以及血清 IL-8、IL-22 及 TNF- α 水平整体比较有统计学差异

($P<0.05$)。重度组患者 SFAR 评分、VAS 评分以及血清 IL-8、IL-22 及 TNF- α 水平均明显高于中度组和轻度组,且中度组明显高于轻度组($P<0.05$)。统计结果见表 2。

表 2 过敏性鼻炎患者 SFAR 评分、VAS 评分以及炎症因子水平比较($\bar{x}\pm s$)

Table 2 Comparison of SFAR score, VAS score and inflammatory factors in patients with allergic rhinitis($\bar{x}\pm s$)

Group	n	SFAR score(points)	VAS score(points)	IL-8(ng/L)	IL-22(ng/L)	TNF- α (ng/L)
Mild	8	1.37 $\pm$ 0.27	1.89 $\pm$ 0.37	10.15 $\pm$ 1.99	5.79 $\pm$ 1.14	6.02 $\pm$ 1.18
Moderate	16	3.49 $\pm$ 0.62 ^a	4.96 $\pm$ 0.89 ^a	16.08 $\pm$ 2.87 ^a	9.77 $\pm$ 1.74 ^a	11.28 $\pm$ 2.01 ^a
Severe	75	7.82 $\pm$ 1.53 ^{ab}	8.74 $\pm$ 1.21 ^{ab}	22.85 $\pm$ 3.46 ^{ab}	14.31 $\pm$ 2.17 ^{ab}	16.50 $\pm$ 2.50 ^{ab}
F		6.719	7.518	8.097	7.564	7.873
P		0.000	0.000	0.000	0.000	0.000

Note: compared with mild group, ^a $P<0.05$; compared with moderate group, ^b $P<0.05$.

2.3 血清 IL-8、IL-22 及 TNF- α 水平与 SFAR 评分和 VAS 评分相关性分析

血清 IL-8、IL-22、TNF- α 水平与 SFAR 评分和 VAS 评分均呈正相关($P<0.05$)。各指标的相关性分析见表 3。

表 3 血清 IL-8、IL-22 及 TNF- α 水平与 SFAR 评分和 VAS 评分相关性分析

Table 3 Correlation analysis of serum IL-8, IL-22 and TNF- levels with SFAR score and VAS score

Index	IL-8		IL-22		TNF- α	
	r	P	r	P	r	P
SFAR score	0.721	0.000	0.698	0.000	0.639	0.000
VAS score	0.723	0.000	0.684	0.000	0.626	0.000

3 讨论

过敏性鼻炎是一种非感染性炎症性疾病,发病过程中患者体内的炎症反应水平明显升高^[17]。临床症状以鼻塞、连续性喷嚏和鼻痒为主,病情严重时会累及周围组织器官,对患者造成严重不良影响^[18]。因此,寻找过敏性鼻炎患者发病的影响因素,对其制定针对性干预措施以降低过敏性鼻炎发病率和改善患者临床症状具有重要意义。

过敏性鼻炎发病过程中患者暴露于过敏原中会导致患者体内过敏原特异性 T 细胞大量增殖,并且浸润到患者的鼻黏膜组织中产生相应的过敏性鼻炎反应^[19]。IL-8 作为一种趋化因子,能够促进 T 细胞的增殖和浸润。例如 Menailo ME 等人^[20]的研究发现 IL-8 能够促进 T 细胞的增殖以及记忆性 T 细胞的产生。同时, Sun L 等人^[21]的研究表明 IL-8 能够活化细胞内的信号转导与转录激活因子 3(Signal transduction and transcriptional activator 3, STAT3)信号通路,进而激活 STAT3 信号通路下游免疫相关蛋白的表达,而 Chen W 等人^[22]的研究结果发现 STAT3 信号通路的活化能够促进 T 细胞的分化和增殖,并且 STAT3 蛋白磷酸化入核后能够结合到辅助性 T 细胞 17(T helper cell 17, TH17)基因的启动子上并上调 TH17 基因,进而促进 T 细胞增殖。本研究结果发现在过敏性鼻炎患者中血清 IL-8 水平明显上调,且其水平与过敏性鼻炎的严重程度相关,并且随患者病情加重而增加。分析其原因可能是由于过敏原特异性 T 细胞的过度增殖是过敏性鼻炎发病过程中的重要环节,患者血清 IL-8 水平升高能够大量活化 T 细胞内的 STAT3 信

号通路,导致过敏原特异性 T 细胞内 TH17 等 T 细胞增殖相关基因的表达明显上调,进而促进过敏原特异性 T 细胞的增殖,大量增殖的过敏原特异性 T 细胞转移至患者的鼻黏膜组织中并引起相应过敏性鼻炎的临床症状^[23]。过敏性鼻炎患者暴露于过敏原中会促进辅助性 T 细胞的增殖和鼻黏膜组织浸润,进而产生相应过敏性鼻炎症状^[24]。IL-22 主要由辅助性 T 细胞、细胞毒性 T 细胞和自然杀伤性细胞分泌产生,辅助性 T 细胞的大量增殖会促进 IL-22 的过度分泌。例如 Voigt C 等人^[25]的研究结果发现辅助性 T 细胞能够分泌产生 IL-22,并且 IL-22 的分泌受到 IL-1 β 的调节。而 Kärner J 等人^[26]的研究表明 T 淋巴细胞中的 IL-22 分泌受到肿瘤生长因子 - β (Tumor growth factor- β , TGF- β)信号通路的调节,抑制 TGF- β 信号通路的活化能够有效降低 IL-22 的产生。本研究结果发现在过敏性鼻炎患者中血清 IL-22 水平明显上调,该结果表明 IL-22 可能参与过敏性鼻炎的发生。进一步结果发现血清 IL-22 水平随患者病情严重程度增加而上调,并且血清 IL-22 水平与 SFAR 评分和 VAS 评分均呈正相关性。分析其原因可能是由于在过敏性鼻炎发病过程中,过敏原能够促进患者体内的辅助性 T 细胞大量增殖,同时激活辅助性 T 细胞中的 TGF- β 信号通路,导致 IL-22 的分泌量大大增加^[27]。

过敏性鼻炎患者暴露于过敏原会促使机体中的 B 淋巴细胞产生大量过敏原特异性免疫球蛋白 E (immunoglobulin E, IgE)抗体,当再次暴露于相关过敏原时,肥大细胞上 IgE 的交联会导致过敏介质的释放,并促进 T 淋巴细胞、嗜酸性粒细胞和嗜碱性粒细胞浸润到鼻黏膜组织,导致后期过敏反应^[28]。

TNF- α 与 B 淋巴细胞的增殖和成熟密切相关, TNF- α 作用于 B 淋巴细胞上的相关受体并激活 B 淋巴细胞, 进而促进 B 淋巴细胞的增殖和分化, 产生大量效应性 B 淋巴细胞, 而效应性 B 淋巴细胞具有抗体分泌功能, 参与体液免疫和炎症反应过程。如 Pala O 等人^[29]的研究表明 TNF- α 参与 B 淋巴细胞的增殖和分化过程, 而 Gui L 等人^[30]的研究表明 TNF- α 能够激活 B 淋巴细胞中细胞外信号调节激酶 (Extracellular Signal Regulated Kinase, ERK) 信号通路, 进而促进 B 淋巴细胞的增殖和成熟。本研究结果表明 TNF- α 可能参与过敏性鼻炎的发生, 且其水平与过敏性鼻炎的严重程度相关, 并且随患者病情加重而增加。分析其原因可能是由于过敏原作用于患者后引起患者体内 TNF- α 水平升高, TNF- α 作用于 B 淋巴细胞并激活 ERK 信号通路, 从而活化 B 淋巴细胞, 导致 B 淋巴细胞大量增殖并分化形成效应性 B 淋巴细胞, 效应性 B 淋巴细胞能够产生大量过敏原特异性 IgE 抗体, 进而促进免疫细胞浸润到鼻粘膜组织, 产生相应过敏性鼻炎症状。

综上所述, 过敏性鼻炎患者血清 IL-8、IL-22 及 TNF- α 水平升高, 并且与病情严重程度、SFAR 评分和 VAS 评分相关, 检测血清 IL-8、IL-22 及 TNF- α 水平可能有助于评估过敏性鼻炎的病情严重程度。

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