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不同严重程度支气管哮喘患者血清 LXA4 水平的表达及临床意义

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摘要 目的:探讨不同严重程度支气管哮喘患者血清脂氧素 A4(LXA4)水平的表达及临床意义。**方法:**选取我院 2015 年 10 月到 2016 年 11 月收治的支气管哮喘患者 86 例作为研究组,另选同期我院体检结果为健康的 40 例志愿者纳入正常对照组,根据病情的不同严重程度将研究组分为轻度持续组(26 例)、中度持续组(36 例)、重度持续组(24 例)。比较正常对照组和研究组患者的血清 LXA4 水平,比较研究组不同严重程度的第 1s 用力呼气量占预计值的百分比(FEV1%),并分析支气管哮喘患者的 LXA4 水平与 FEV1%的相关性。**结果:**轻度持续组、中度持续组、重度持续组和正常对照组血清中 LXA4 水平整体比较差异有统计学意义($P<0.05$);中度持续组血清中 LXA4 水平显著高于轻度持续组、重度持续组和正常对照组,重度持续组血清中 LXA4 水平显著高于轻度持续组和正常对照组,轻度持续组血清中 LXA4 水平显著高于正常对照组,差异有统计学意义($P<0.05$);轻度持续组、中度持续组、重度持续组的 FEV1%整体比较差异有统计学意义($P<0.05$);重度持续组的 FEV1%显著低于轻度持续组和中度持续组,中度持续组的 FEV1%显著低于轻度持续组,差异有统计学意义($P<0.05$);经 Spearman 统计分析,支气管哮喘患者的 LXA4 水平与 FEV1%呈明显的负相关($r=-0.486, P=0.041$)。**结论:**LXA4 在支气管哮喘中度持续患者血清中表达最高,在轻度持续患者血清中表达最低,支气管哮喘越严重 FEV1%水平越低,同时 LXA4 水平与 FEV1%呈明显的负相关。

关键词:支气管哮喘;血清脂氧素 A4;表达;临床意义

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Expression and Clinical Significance of Serum LXA4 Levels in Patients with Different Severity of Bronchial Asthma

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ABSTRACT Objective: To investigate the expression and clinical significance of serum lipoprotein A4 (LXA4) levels in patients with different severity of bronchial asthma. **Methods:** A total of 86 patients with bronchial asthma, who were admitted to Baoji Traditional Chinese Medicine Hospital of Shaanxi Province from October 2015 to November 2016, were chosen as study group; 40 healthy volunteers were included in control group during the same period. According to the severity of the disease, the study group was further divided into mild persistent group ($n=26$), moderate persistent group ($n=36$), severe persistent group ($n=24$). The serum LXA4 levels were compared between the control group and the study group. The percentage of forced expiratory volume as estimated at 1s (FEV1%) at the different severity levels in the study group was compared. The correlation between LXA4 and FEV1% in patients with bronchial asthma was analyzed. **Results:** There were significant differences in the serum LXA4 levels among the mild persistent group, moderate persistent group, severe persistent group and control group ($P<0.05$); the serum LXA4 levels in moderate persistent group were significantly higher than those in mild persistent group, severe persistent group and control group; the serum LXA4 levels in the severe persistent group was significantly higher than those in the mild persistent group and the control group; the serum LXA4 levels in the mild persistent group was significantly higher than that in the control group, the differences were statistically significant ($P<0.05$). There were significant differences in FEV1% among mild persistent group, moderate persistent group and severe persistent group ($P<0.05$); FEV1% in the severe persistent group was significantly lower than those in the mild persistent group and the moderate persistent group; FEV1% in the moderate persistent group was significantly lower than that in mild persistent group, the differences were statistically significant ($P<0.05$). Spearman analysis showed that there was a significant negative correlation between LXA4 and FEV1% ($r=-0.486, P=0.041$) in patients with bronchial asthma. **Conclusion:** LXA4 is the highest expressed in the serum of patients with moderate persistent bronchial asthma, but it is the lowest expressed in the serum of patients with mild persistent bronchial asthma. The more severe the bronchial asthma is, the lower the FEV1% level is; at the same time, the LXA4 level is negatively correlated with FEV1%.

Key words: Bronchial asthma; Serum lipoprotein A4; Expression; Clinical significance

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前言

支气管哮喘是一种由嗜酸性粒细胞、T淋巴细胞、中性粒细胞等多种细胞共同参与的慢性炎症性气道疾病,慢性炎症可增加气道高反应,患者通常表现为多变的可逆性气流受限,其临床症状为反复性发作的气急、喘息、咳嗽、胸闷等,通常在清晨和夜间发作,大部分患者的症状可自行缓解^[1-3]。相关报道^[4],随着环境的恶化和生活习惯的改变,我国支气管哮喘患者数量呈逐年上升的趋势,形势十分严峻,因此探索与支气管哮喘有关的指标具有重大的临床意义。血清脂氧素(LX)是花生四烯酸的一类脂氧化酶产物,主要包括血清脂氧素 A4(LXA4)和 LXB4,其中 LXA4 能对气管内的高气道反应产生抑制作用,且可以通过多种信号通路来抑制炎症反应^[5-7]。本研究旨在探讨不同严重程度支气管哮喘患者血清 LXA4 水平的表达及临床意义,分析支气管哮喘患者的 LXA4 与其第 1s 用力呼气量占预计值的百分比(FEV1%)的相关性,以期更加深入的了解 LXA4 与支气管哮喘患者病情的联系,现将研究结果整理如下。

1 资料与方法

1.1 一般资料

选取我院 2015 年 10 月到 2016 年 11 月收治的支气管哮喘患者 86 例作为研究组,纳入标准:① 所有患者均符合中华医学会呼吸病学分会哮喘学组制定的《支气管哮喘防治指南》中关于支气管哮喘的诊断标准^[8],即存在反复发作的喘息、胸闷或咳嗽,病情发作时双肺可闻以呼气相为主的哮鸣音,且上述症状可自行缓解;② 患者及其家属对本次研究知情同意,且签署了知情同意书。排除标准:① 合并有其他呼吸道或呼吸系统疾病者;② 合并有免疫系统疾病者;③ 妊娠期或哺乳期妇女;④ 不配合本次研究者。所有患者中,男 46 例,女 40 例,年龄 18-63 岁,平均(41.7±14.8)岁,病程 4 个月-21 年,平均病程(2.4±0.6)年。另选同期我院体检结果为健康的 40 例志愿者纳入正常对照组,其中男 22 例,女 18 例,年龄 18-64 岁,平均(42.1±14.9)岁。两组受试者在年龄和性别上没有明显的差异(P>0.05),可作组间比较。本次研究已通过医院伦理委员会的审核。

1.2 不同严重程度支气管哮喘分级标准

本次研究的支气管哮喘患者均为首次病发或既往已确诊但已长时间未接受药物治疗。根据《支气管哮喘防治指南》对治

疗前支气管哮喘的病情程度进行分级,轻度持续:发作次数超过每周 1 次,但未达到每天 1 次,对正常的活动和睡眠会造成一定的影响,夜间发作超过每个月 2 次,但未达到每周 1 次,FEV1%大于 80%或者最大呼气流量(PEF)大于个人最佳值的 80%;中度持续:发作次数达到每天 1 次,对正常的活动和睡眠会造成较大的影响,夜间发作超过每周 1 次,FEV1%在 60%~79%之间,或者 PEF 在个人最佳值的 60%~79%之间;重度持续:发作次数超过每天 1 次,并且频繁发作,夜间发作次数频繁,对正常的活动和睡眠会造成严重的影响,体力活动受限,FEV1%小于 60%或者 PEF 小于个人最佳值的 60%。根据上述标准将研究组患者分为轻度持续组(26 例)、中度持续组(36 例)、重度持续组(24 例)。

1.3 检测指标

抽取所有受试者的空腹静脉血 5 mL,装入采血试管内,以 5000 r/min 的转速离心 10 min,收集上清液,将其装入试管并标记好受试者的信息,置于 -80℃ 的环境下保存待测。所有受试者血清中 LXA4 水平采用酶联免疫吸附试验法进行测定,LXA4 试剂盒购自上海信帆生物科技有限公司,所有检测步骤均严格参照试剂盒说明书中的操作指南进行。采用肺功能仪检测研究组患者的肺功能,患者将吹气口用口含住,同时捏住鼻子,数次平静呼吸后进行最大吸气,屏气 1s 后用最大力气进行快速呼气,测定 FEV1%。

1.4 统计学方法

所有数据均用 SPSS19.0 进行统计分析,计数资料以率(%)的形式表示,采用卡方检验,计量资料以($\bar{x} \pm s$)的形式表示,多组间比较采用方差分析,两两比较采用 t 检验,采用 Spearman 进行相关性分析,以 P<0.05 为差异有统计学意义。

2 结果

2.1 研究组和正常对照组血清中 LXA4 水平比较

轻度持续组、中度持续组、重度持续组和正常对照组血清中 LXA4 水平整体比较差异有统计学意义(P<0.05);中度持续组血清中 LXA4 水平显著高于轻度持续组、重度持续组和正常对照组,重度持续组血清中 LXA4 水平显著高于轻度持续组和正常对照组,轻度持续组血清中 LXA4 水平显著高于正常对照组,差异有统计学意义(P<0.05),详见表 1。

表 1 研究组和正常对照组血清中 LXA4 水平比较

Table 1 Comparison of serum LXA4 levels between study group and control group

Groups	n	LXA4(ng/L)
Normal control group	40	180.39±16.88 ^{bc}
Mild persistent group	26	232.45±21.14 ^{ac}
Study group		
Moderate persistent group	36	297.63±33.22 ^{ab}
Severe persistent group	24	274.65±25.46 ^{abc}
F	-	89.647
P	-	0.000

Note: compared with the normal control group, ^aP<0.05; compared with mild persistent group, ^bP<0.05; compared with moderate persistent group, ^cP<0.05.

2.2 不同严重程度支气管哮喘患者 FEV1%比较

轻度持续组、中度持续组、重度持续组的 FEV1%整体比较

差异有统计学意义(P<0.05);重度持续组的 FEV1%显著低于轻度持续组和中度持续组,中度持续组的 FEV1%显著低于轻

度持续组,差异有统计学意义($P<0.05$),详见表 2。

表 2 不同严重程度支气管哮喘患者 FEV1%比较

Table 2 Comparison of FEV1% in patients with different severity of bronchial asthma

Groups	n	FEV1%
Mild persistent group	26	81.56± 8.56
Moderate persistent group	36	67.43± 11.24 ^b
Severe persistent group	24	51.35± 8.28 ^{bc}
F	-	67.684
P	-	0.000

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

2.3 支气管哮喘患者的 LXA4 水平与其 FEV1%的相关性分析

经 Spearman 统计分析,支气管哮喘患者的 LXA4 水平与 FEV1%呈明显的负相关($r=-0.486$, $P=0.041$)。

3 讨论

支气管哮喘是一种最为常见的呼吸道疾病之一,患者会出现支气管平滑肌肥大收缩、中性粒细胞和嗜酸粒细胞浸润、基底膜增厚,小支气管黏膜出现水肿且腺体分泌增多,导致黏液栓的形成,气道变狭窄,进而导致患者出现气急、呼吸困难等症状^[9-11]。虽然通过合理的治疗可以较好的控制支气管哮喘患者的病情,但目前的治疗手段尚不能根治,因此探究和支气管哮喘相关的指标,寻找根治性治疗方法是目前的研究热点^[12-14]。引起支气管哮喘的病发的原因复杂多变,其中以食入性或吸入性变应原、呼吸道出现病毒感染为较为常见且致病能力强的原因^[15,16]。据相关研究报道^[17,18],支气管哮喘患者的主要危险因素有家族疾病史、神经调节功能紊乱、免疫功能紊乱、炎性细胞和炎症介质等,其中炎性细胞和炎症介质对支气管哮喘影响的研究较为深入,嗜酸性粒细胞、肥大细胞、中性粒细胞、嗜碱性粒细胞、活化的血小板等多种细胞因子均参与了气道炎症的发生、发展,同时多种因子也参与了炎症反应的调节,LXA4 便是其中一种重要的炎症反应调节因子,具有较强的抑制炎症反应和促炎症症状消退的作用^[19,20]。本研究通过对比不同严重程度的支气管哮喘患者血清 LXA4 水平,以探讨 LXA4 与支气管哮喘患者病情的联系,为临床研究提供参考。

本次研究结果显示,轻度持续组、中度持续组、重度持续组的 FEV1%整体比较差异有统计学意义($P<0.05$);重度持续组的 FEV1%显著小于轻度持续组和中度持续组,中度持续组的 FEV1%显著小于轻度持续组,差异有统计学意义($P<0.05$)。这说明随着病情的加重,FEV1%水平逐渐降低,FEV1%是临床上衡量支气管哮喘的一个常用指标,由于支气管哮喘患者气道狭窄,存在一定程度的呼吸困难,且病情越重气道狭窄越明显,进而降低了 FEV1%值。同时研究发现,轻度持续组、中度持续组、重度持续组和正常对照组血清中 LXA4 水平整体比较差异有统计学意义($P<0.05$);中度持续组血清中 LXA4 水平显著高于轻度持续组、重度持续组和正常对照组,重度持续组血清中 LXA4 水平显著高于轻度持续组和正常对照组,轻度持续组血清中 LXA4 水平显著高于正常对照组,差异有统计学意义($P<0.05$),这说明了 LXA4 在支气管哮喘患者血清中呈现高表达,同时表达水平和患者的疾病严重程度有关,值得注意的是,

LXA4 和疾病严重程度并非呈简单的线性关系,而是在中度持续的患者中表达最高,轻度持续的患者表达最低^[21-23]。究其原因,LXA4 是人体内重要的抑制炎症反应和促炎症症状消退的介质,通过与其受体(ALX)结合,可抑制中性粒细胞的聚集,同时促进清除凋亡的中性粒细胞,对促炎因子和抗炎因子的平衡起到调节作用,同时能限制炎症损伤^[24,25]。当患有支气管哮喘后,患者气道内出现不同程度的炎症反应,机体通过外周血巨噬细胞和肺泡巨噬细胞来产生 LXA4,LXA4 可以通过 p24/44MAPK 通路、PI3K/Akt 通路、多萜醇磷酸途径来抑制炎症反应,当病情更为严重时,机体应激产生更多 LXA4 来对炎症反应进行调节,因此中度持续患者的 LXA4 表达水平较高。另一方面,LXA4 可以激活自然杀伤细胞,从而导致机体的免疫反应降低,因此 LXA4 过高表达可对免疫功能造成抑制作用,因此可以推测,在重度持续患者中机体控制了 LXA4 的水平,以达到免疫功能和炎症调节能力的平衡^[26-28]。同时研究还发现,支气管哮喘患者的 LXA4 水平与 FEV1%呈明显的负相关,说明 LXA4 水平和支气管哮喘患者的肺功能具有一定的关联,和相关研究结果一致^[29,30]。

综上所述,在支气管哮喘患者中,LXA4 在中度持续患者血清中表达最高,在轻度持续患者血清中表达最低,支气管哮喘月严重 FEV1%水平越低,同时 LXA4 水平与 FEV1%呈明显的负相关。

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