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哮喘患儿呼出气一氧化氮、1,25-二羟维生素 D₃ 及儿童哮喘控制测试评分与肺功能的相关性*

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摘要 目的:探讨哮喘患儿呼出气一氧化氮(FeNO)、1,25-二羟维生素 D₃[1,25(OH)₂D₃]及儿童哮喘控制测试(C-ACT)评分与肺功能的相关性。**方法:**选取 2017 年 6 月~2018 年 6 月在我院就诊的 86 例哮喘患儿作为观察组,另选取同期于我院进行健康检查的 86 例健康儿童作为对照组。比较两组受试儿童 1,25(OH)₂D₃ 浓度、FeNO、一秒用力呼气容积(FEV1)、呼气流量峰值(PEF)水平,比较不同病情哮喘患儿 1,25(OH)₂D₃ 浓度、FeNO、C-ACT、FEV1、PEF 水平,并分析哮喘患儿 1,25(OH)₂D₃、FeNO、C-ACT 与肺功能的相关性。**结果:**观察组 1,25(OH)₂D₃ 浓度、FEV1、PEF 水平低于对照组($P<0.05$),FeNO 水平高于对照组($P<0.05$);随着病情加重,1,25(OH)₂D₃ 浓度、PEF、FEV1 水平、C-ACT 评分均逐渐下降,FeNO 水平逐渐升高,不同病情患儿间比较差异均有统计学意义($P<0.05$)。哮喘患儿 1,25(OH)₂D₃ 与 FEV1、PEF 呈正相关($r=0.912, 0.873, P=0.006, 0.008$);C-ACT 与 FEV1、PEF 呈正相关($r=0.472, 0.366, P=0.036, 0.032$);FeNO 与 FEV1、PEF 无相关($r=-0.035, -0.124, P=0.075, 0.064$)。**结论:**哮喘患儿 1,25(OH)₂D₃ 浓度、C-ACT 评分明显降低,FeNO 水平明显升高,1,25(OH)₂D₃、C-ACT 评分与肺功能呈正相关,但 FeNO 与肺功能无相关,C-ACT 可用于哮喘患儿病情的预测,同时,通过提高患儿体内 1,25(OH)₂D₃ 浓度可以改善其肺功能。

关键词:哮喘;患儿;肺功能;呼出气一氧化氮;儿童哮喘控制测试;1,25-二羟维生素 D₃;相关性

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Correlation between FeNO, 1,25(OH)₂D₃, C-ACT Scores and Pulmonary Function in Children with Asthma*

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ABSTRACT Objective: To explore the correlation between fractional exhaled nitric oxide (FeNO), 1, 25-dihydroxyvitamin D₃[1,25(OH)₂D₃], children asthma control test (C-ACT) scores and pulmonary function in children with asthma. **Methods:** 86 children with asthma in our hospital from June 2017 to June 2018 were selected as the observation group, and another 86 healthy children who were received physical examination in our hospital during the same period were selected as control group. The concentrations of 1, 25(OH)₂D₃, levels of FeNO, forced expiratory volume in one second (FEV1) and peak expiratory flow (PEF) were compared between the two groups. The concentrations of 1,25 (OH)₂D₃, levels of FeNO, C-ACT, FEV1 and PEF in children with different stages of disease were compared. The correlation between 1,25 (OH)₂D₃, FeNO, C-ACT and pulmonary function in children with asthma was analyzed. **Results:** The concentration of 1,25 (OH)₂D₃ and the levels of PEF, FEV1 in observation group were significantly lower than those of the control group ($P<0.05$), while the level of FeNO was significantly higher over than that of the control group ($P<0.05$). With the aggravation of the patient's condition, the concentrations of 1,25 (OH)₂D₃, levels of PEF, FEV1, C-ACT scores were decreased gradually, while the level of FeNO was increased gradually, and the differences were statistically significant between children in different status($P<0.05$). 1,25(OH)₂D₃ in children with asthma was positively correlated with FEV1, PEF ($r=0.912, 0.873, P=0.006, 0.008$). C-ACT was positively correlated with FEV1, PEF ($r=0.472, 0.366, P=0.036, 0.032$). FeNO was not correlated with FEV1, PEF ($r=-0.035, -0.124, P=0.075, 0.064$). **Conclusion:** The concentrations of 1,25 (OH)₂D₃ and C-ACT scores in children with asthma are significantly decreased, and the level of

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FeNO is increased significantly. 1, 25 (OH)₂D₃ and C-ACT scores are positively correlated with lung function, but FeNO is not correlated with lung function. C-ACT can be used to predict the condition of children with asthma, at the same time, lung function of children with asthma can be improved by increasing the concentration of 1,25(OH)₂D₃.

Key words: Asthma; Children; Pulmonary function; Fractional exhaled nitric oxide; Children asthma control test; 1,25-dihydroxyvitamin D₃; Correlation

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前言

支气管哮喘属于常见慢性呼吸道疾病之一,在我国儿童中发病率较高,且发病率和死亡率呈上升趋势^[1],给儿童的生活、学习造成一定的影响,同时给患儿的家庭也带来沉重的经济负担。支气管镜活检法和诱导痰嗜酸性粒细胞计数法是目前哮喘诊断中常用的两种方法,但由于两种方法创伤性都较大、费用也较高,导致其在临床应用上受到限制,因此寻找无创、简便的哮喘评估指标十分必要^[2,3]。目前大量研究表明^[4-6],呼出气一氧化氮(Fractional exhaled nitric oxide, FeNO)与诱导痰嗜酸性粒细胞计数相关,且具有无创、可重复、准确性高等优点,因此其能够作为评价气道炎症的间接指标。儿童哮喘控制测试(Children asthma control test, C-ACT)是评估哮喘病情的新工具,具有对病情变化感应迅速、操作简单、经济实用、易于被患儿接受等特点^[7]。1,25-二羟维生素 D₃[1,25-dihydroxy vitamin D₃, 1,25 (OH)₂D₃]可以调节体内的钙磷平衡,同时在哮喘治疗中发挥着免疫调节、抗炎以及影响气道重塑的作用^[8,9]。本研究选取我院就诊的 86 例哮喘患儿为研究对象,通过对患儿 FeNO、肺功能、1,25 (OH)₂D₃ 的检测以及 C-ACT 评分的测定,分析肺功能与 FeNO、1,25(OH)₂D₃、C-ACT 的相关性,旨在为临床哮喘的诊治提供理论依据,现将结果报道如下。

1 资料与方法

1.1 一般资料

选取 2017 年 6 月~2018 年 6 月在我院就诊的 86 例哮喘患儿作为观察组。纳入标准:(1)所有患儿符合 2016 年儿童哮喘诊疗规范与防治指南的诊断标准^[10];(2)年龄不超过 13 岁,能够配合相关检查;(3)患儿家属对本研究均知情同意。排除标准:(1)指标测定 6h 前食用过动物内脏、菠菜、香肠等富含氮类食物者;(2)经常饮用含咖啡因的饮料者;(3)入组前 1 个月内服用过静脉糖皮质激素者;(4)心肺肾等功能不全、患有精神疾病、过敏性炎症患儿。其中男 52 例,女 34 例,年龄 4~12 岁,平均(7.25±2.39)岁,病程 7 个月~5 年,平均(24.38±8.19)个月,按照 2014 版全球哮喘防治倡议(Global INitiative for Asthma, GINA)评定的哮喘分级标准^[11],其中间歇状态者 55 例,轻度持续者 19 例,中度持续者 7 例,重度持续者 5 例。另选取同期于我院进行健康体检的 86 例健康儿童作为对照组,其中男 56 例,女 30 例,年龄 3~13 岁,平均年龄(7.64±3.16)岁,两组研究对象在性别、年龄间的比较差异无统计学意义($P>0.05$),具有可比性。本研究经我院伦理委员会批准进行。

1.2 方法

患儿在专业医生指导下与家长一起填写 C-ACT 问卷,问

卷包含 7 个问题,前 4 个问题在家长帮助阅读理解后由患儿自己选择答案,包括你觉得哮喘怎么样、在运动时哮喘是个多大的问题、哮喘是否会引起咳嗽以及在夜里你是否会因为哮喘而醒来,答案设置 4 个等级(0~3 分);后 3 个问题由家长回答,包括过去 4 周内白天出现多少次哮喘症状、有多少次白天发生哮喘时患儿出现喘息声、有多少次患儿因为哮喘在夜间醒来,答案设置 5 个等级(1~5 分),问卷总分 0~27 分,填写后由医生统计核对分数。

所有受试儿童于空腹状态下进行静脉抽血 3 mL,以 3500 r/min 的速度离心 10 min 后分离上层血清,采用酶联免疫法测定两组血清中 1,25(OH)₂D₃ 浓度(酶联免疫试剂盒购自于 Thermo Fisher Scientific 公司),参照试剂盒说明书进行操作,记录测定结果。

采用 Thermo Scientific™ 42i 型一氧化氮(Nitric oxide, NO)分析仪在受试儿童安静状态下测定 FeNO 水平,所有操作严格按照产品说明书进行,测定结果分析参照欧洲呼吸学会或美国胸科学会制定的 FeNO 标准^[12],并以 ppb(parts per billiOn)为单位进行记录。

FeNO 测定结束后进行肺功能测定,测定仪器为康讯 Power Cube 型肺功能仪,按照仪器测定说明进行操作,分别测定受试儿童最大呼吸峰流速(Peak expiratory flow, PEF)及第一秒用力呼气容积(Forced expiratory volume in one second, FEV1),每位受试儿童均测定 3 次,各指标最后结果为 3 次的平均值。

1.3 观察指标

(1)对比两组血清中 1,25(OH)₂D₃ 浓度、FeNO 及肺功能水平;(2)分析不同病情哮喘患儿血清中 1,25 (OH)₂D₃ 浓度、FeNO 水平、C-ACT 评分及肺功能情况;(3)分析哮喘患儿血清 1,25(OH)₂D₃、C-ACT 评分及 FeNO 与肺功能的相关性。

1.4 统计学分析

本研究数据采用 SPSS19.0 进行统计分析,计数资料用率表示,采用检验,1,25(OH)₂D₃ 浓度、C-ACT 评分、FeNO、肺功能指标水平等计量资料用均数± 方差表示,采用 t 检验,采用 Person 相关性分析分析哮喘患儿血清 1,25(OH)₂D₃、C-ACT 评分及 FeNO 与肺功能的相关性,检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 两组 1,25(OH)₂D₃、FeNO 及肺功能分析

观察组 1,25 (OH)₂D₃ 浓度、FEV1、PEF 水平低于对照组($P<0.05$),FeNO 水平高于对照组($P<0.05$),详见表 1 所示。

2.2 不同病情哮喘患儿 1,25 (OH)₂D₃、FeNO、C-ACT 及肺功能指标情况

不同病情哮喘患儿 1,25 (OH)₂D₃ 浓度、FeNO、C-ACT 评

分、PEF、FEV1 水平整体比较差异有统计学意义($P<0.05$),随着患儿病情加重,1,25 (OH)₂D₃ 浓度、C-ACT 评分、PEF、FEV1 水平平均逐渐下降,FeNO 水平逐渐升高,不同病情患儿间差异均有统计学意义($P<0.05$),详见表 2 所示。

表 1 两组 1,25(OH)₂D₃、FeNO 及肺功能对比($\bar{x}\pm s$)

Table 1 Comparison of 1,25 (OH)₂D₃, FeNO and pulmonary function in two groups($\bar{x}\pm s$)

Groups	n	1,25 (OH) ₂ D ₃ (ng/mL)	FeNO(ppb)	FEV1(%)	PEF(%)
Observation group	86	22.58± 7.26	37.15± 4.64	56.34± 6.98	52.36± 9.76
Control group	86	45.16± 10.43	8.94± 2.68	98.65± 8.36	85.28± 10.71
t		16.478	48.823	36.027	21.069
P		0.000	0.000	0.000	0.000

表 2 不同病情哮喘患儿 1,25(OH)₂D₃、FeNO、C-ACT 及肺功能指标对比($\bar{x}\pm s$)

Table 2 Comparison of 1,25 (OH)₂D₃, FeNO, C-ACT and pulmonary function in children with different conditions of asthma($\bar{x}\pm s$)

Groups	n	1,25 (OH) ₂ D ₃ (ng/mL)	FeNO(ppb)	C-ACT(score)	PEF(%)	FEV1(%)
Intermittent state stage	55	33.67± 7.65	19.75± 7.36	23.35± 6.74	81.25± 8.13	79.25± 13.62
Mild continuous stage	19	27.97± 6.14 [#]	27.56± 13.24 [#]	19.54± 7.68 [#]	71.65± 11.67 [#]	68.94± 4.49 [#]
Moderate continuous stage	7	22.38± 8.42 ^{ab}	32.94± 11.67 ^{ab}	16.38± 6.29 ^{ab}	60.28± 15.37 ^{ab}	56.49± 16.73 ^{ab}
Severe continuous stage	5	16.34± 4.68 ^{ab}	40.28± 15.34 ^{ab}	11.58± 4.54 ^{ab}	42.68± 16.75 ^{ab}	39.27± 11.53 ^{ab}
F		13.431	10.855	6.641	29.052	21.827
P		0.000	0.000	0.001	0.000	0.000

Note: compared with intermittent state stage, [#] $P<0.05$, compared with mild continuous stage, ^a $P<0.05$, compared with moderate continuous stage, ^b $P<0.05$.

2.3 哮喘患儿 1,25 (OH)₂D₃、C-ACT 评分及 FeNO 与肺功能的相关性

通过 Person 相关性分析显示,哮喘患儿 1,25 (OH)₂D₃ 与 PEF、FEV1 呈正相关($r=0.873$ 、 0.912 , $P=0.008$ 、 0.006),如图所

示 1(a)、1(b)所示。哮喘患儿 C-ACT 与 FEV1、PEF 呈正相关($r=0.472$ 、 0.366 , $P=0.036$ 、 0.032),如图 2(a)、2(b)所示。哮喘患儿 FeNO 与 FEV1、PEF 无相关($r=-0.035$ 、 -0.124 , $P=0.075$ 、 0.064),如图 3(a)、3(b)所示。

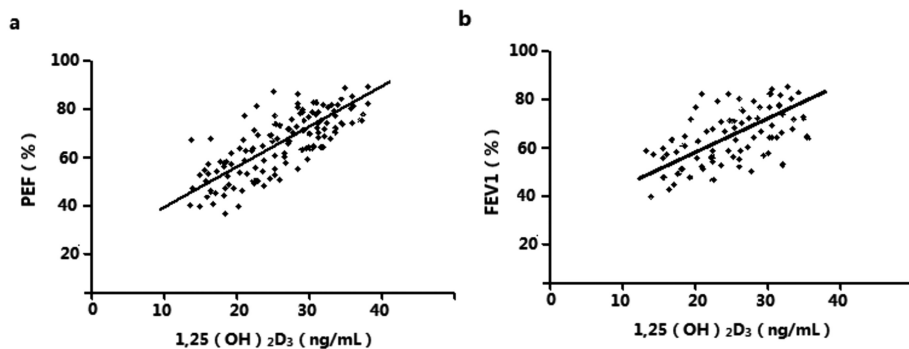


图 1 1,25(OH)₂D₃ 与肺功能指标相关性

Fig. 1 Correlation between 1,25(OH)₂D₃ and pulmonary function indexes

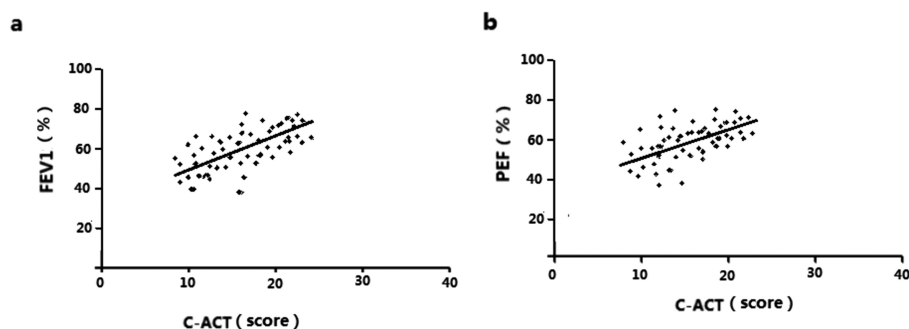


图 2 C-ACT 与肺功能指标相关性

Fig. 2 Correlation between C-ACT and pulmonary function indexes

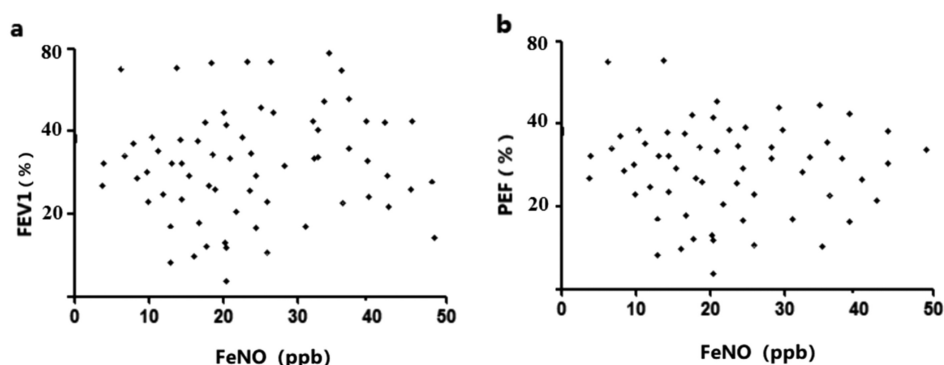


图3 FeNO与肺功能指标相关性

Fig. 3 Correlation between FeNO and pulmonary function indexes

3 讨论

哮喘主要是由于细胞因子、炎性细胞、黏附因子等对患者造成气道炎性损伤,而气道炎性损伤将导致气道狭窄,从而使气道内吸入的刺激物沉积,进而引发非特异性气道炎症^[13,14]。哮喘发病机制为气道上皮受损后释放大量的透明质酸酶,而透明质酸酶会破坏内皮细胞结缔组织,从而使得刺激物更容易接近气道上的受体,进而导致气道高反应性^[15,16]。当气道通气受阻时,患者表现为FEV1、PEF水平下降,因此通过测定肺功能指标FEV1、PEF水平能够反应哮喘患者病情的严重程度^[17,18]。FeNO是由上皮细胞中的一氧化氮合酶合成,机体内大部分细胞能够产生FeNO,有研究表明^[19],机体内FeNO水平的变化与呼吸系统疾病病情变化密切相关。1,25(OH)₂D₃是维生素D₃的主要生物作用形式,其在血清内的浓度高低可以作为评价机体内维生素营养状况的标准,有报道显示^[20],1,25(OH)₂D₃参与了哮喘的发病。C-CAT评分是用于评估哮喘患儿病情严重程度的简易而有效的工具,通过对患儿C-CAT评分的评估,可以判定哮喘的控制水平^[21]。

相关研究表明^[22],哮喘儿童中FeNO水平显著高于健康儿童,且哮喘越严重FeNO水平越高,同时在患有鼻炎或其它过敏性鼻炎患儿中,FeNO水平高于无过敏性鼻炎患儿,说明FeNO将影响哮喘患儿病情的进展。在本研究中纳入的患儿均无过敏性鼻炎,通过测定结果显示,哮喘患儿FeNO水平高于健康儿童,且随着哮喘病情加重,FeNO水平也相应升高,与上述文献报道结果相符。此外,FeNO能够反应气道炎症,而肺功能损伤是气道阻塞的表现形式,有研究表明,两者间存在相关性^[23]。而本研究结果显示,FeNO与肺功能FEV1、PEF无相关,分析原因可能为哮喘患儿年纪较小,肺功能水平还未达到成年人水平,从而可能导致测定中数据有所误差,进而造成相关性分析结果存在差异。1,25(OH)₂D₃是维生素D₃活性代谢产物,人体内摄入1,25(OH)₂D₃能够防止气道过敏,且有益于肺功能^[24,25]。有研究证明,1,25(OH)₂D₃在调控哮喘引起的免疫应答及炎症反应过程中发挥着重要作用^[26]。本研究结果显示,哮喘患儿血清中1,25(OH)₂D₃浓度低于对照组,且随着哮喘病情的加重,血清1,25(OH)₂D₃浓度也不断下降,说明哮喘患儿1,25(OH)₂D₃可以影响病情的发展,这可能与1,25(OH)₂D₃能够降低气道炎症反应、影响气道重塑以及调节免疫细胞因子水平有关。在Th2细胞作用下,哮喘患儿体内

产生大量的嗜酸性细胞、炎症因子、B细胞等,进一步引发气道炎症,而1,25(OH)₂D₃可以抑制Th2细胞活性,从而抑制炎症相关因子的产生,以达到抗炎以及增强免疫应答的作用,因此当哮喘患儿体内1,25(OH)₂D₃浓度降低时,其病情也将加重^[27-29]。此外,本研究相关性结果显示,1,25(OH)₂D₃与肺功能相关指标PEF、FEV1均呈显著正相关,提示可以通过提高1,25(OH)₂D₃浓度对患儿肺功能起到保护作用。C-CAT是评估患儿近4周哮喘控制状况的问卷测试,近年来调查显示,C-CAT与PEF、FEV1间有相关性^[30],本研究结果也显示,哮喘患儿C-CAT与FEV1、PEF呈正相关,表明当哮喘患儿通气功能降低时,FEV1、PEF水平升高,此时C-CAT评分也升高,C-CAT评分能准确反映哮喘患儿病情。

综上所述,哮喘患儿1,25(OH)₂D₃、C-CAT与肺功能FEV1、PEF呈正相关,FeNO与肺功能无相关,且随着哮喘患儿病情严重程度增加,1,25(OH)₂D₃浓度、C-CAT评分呈现明显下降趋势,C-CAT可用于哮喘患儿病情的预测,通过给哮喘患儿补充1,25(OH)₂D₃可以改善肺功能,控制病情。由于本研究患儿病例数量有限,同时对患儿过敏体质等未进行深入研究,因此FEV1、PEF与FeNO、C-CAT、1,25(OH)₂D₃之间的相关性还有待更多实验进一步深入研究。

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