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呼出气一氧化氮浓度与儿童哮喘病情控制及不同哮喘亚型的相关性研究*

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摘要 目的:探讨呼出气一氧化氮(FeNO)浓度与儿童哮喘病情控制及不同哮喘亚型的相关性。**方法:**选取2017年1月至2018年1月期间于我院确诊为支气管哮喘及毛细支气管炎的患儿各60例,分别设为哮喘组与毛细支气管炎组,另选取同期于我院进行体检的健康儿童40例作为对照组。哮喘组与毛细支气管炎组分别在治疗前、治疗后1 h及治疗后4周测定FeNO,对照组在体检时测定FeNO。对比对照组体检时以及哮喘组、毛细支气管炎组患儿不同治疗时期的FeNO浓度变化;哮喘组患儿根据不同病情控制情况分为哮喘控制组、哮喘部分控制组与哮喘未控制组，根据不同哮喘亚型分为咳嗽变异性组与非咳嗽变异性组，分析FeNO与哮喘患儿疾病控制情况、哮喘亚型的相关性。**结果:**哮喘组治疗前的FeNO浓度高于毛细支气管炎组治疗前和对照组体检时的FeNO浓度(P<0.05);与治疗前与治疗后1 h比较,治疗4周后哮喘组与毛细支气管炎组患儿FeNO浓度降低(P<0.05),治疗后1 h及治疗4周后哮喘组FeNO浓度高于毛细支气管炎组(P<0.05)。哮喘控制组FeNO浓度低于部分控制组与哮喘未控制组,哮喘部分控制组FeNO浓度低于哮喘未控制组,咳嗽变异性组FeNO浓度高于非咳嗽变异性组(P<0.05)。FeNO浓度与病情控制呈负相关,FeNO浓度越低,病情控制程度越好(r= -0.512,P=0.034)。**结论:**哮喘患儿的FeNO浓度高于毛细支气管炎患儿、健康儿童,且与患儿哮喘的病情控制存在相关性,可作为哮喘患儿的辅助诊断指标。

关键词:呼出气一氧化氮;儿童;哮喘;相关性

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Study on the Relationship between Fractional Exhaled Nitric Oxide, Asthma Control in Children and Different Subtypes of Asthma*

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ABSTRACT Objective: To investigate the correlation between fractional exhaled nitric oxide (FeNO), asthma control in children and different subtypes of asthma. **Methods:** 60 children with bronchial asthma and bronchiolitis who were diagnosed in our hospital from January 2017 to January 2018 were selected. They were divided to asthma group and bronchiolitis group. In addition, 40 healthy children who underwent physical examination for non-respiratory diseases in the same period in our hospital were selected as the control group. The FeNO of asthma group and bronchiolitis group were measured before treatment, 1 h after treatment and 4 weeks after treatment. FeNO was measured in the control group at the time of physical examination. The changes of FeNO concentration in control group at the time of physical examination, asthma group and bronchiolitis group at different stages of treatment were compared. children in the asthma group were divide into the asthma controlled group, asthma part controlled group and asthma uncontrolled group according to their asthma control status, and divided into cough variant group and non-cough variant group according to their asthma subtypes. The correlation between FeNO, asthma control and asthma subtypes in children with asthma were analyzed. **Results:** The concentration of FeNO in asthma group before treatment was higher than that in bronchiolitis group before treatment and control group at the time of physical examination(P<0.05). Compared with before and 1 h after treatment, the concentration of FeNO in asthmatic group and bronchiolitis group decreased significantly at 4 weeks after treatment (P<0.05). The concentration of FeNO in asthma group was higher than that in bronchiolitis group 1 h after treatment and 4 weeks after treatment (P<0.05). The concentration of FeNO in asthma controlled group were significantly lower than asthma part controlled group and asthma uncontrolled group. The concentration of FeNO in asthma part controlled group was lower than that in asthma uncontrolled group. The concentration of FeNO in cough variance group was higher than that in non-cough variance group (P<0.05). The concentration of FeNO was negatively correlated with disease control, the lower the concentration of FeNO, the better the disease controlled (r=-0.512, P=0.034). **Conclusion:** The concentration of FeNO in children with asthmatic was significantly higher than that in children with bronchiolitis and healthy children. It has correlation with asthma control, and can be used as an auxiliary diagnostic index for children with asthma.

Key words: Fractional exhaled nitric oxide; Infant; Asthma; Correlation

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前言

支气管哮喘是儿童常见的慢性呼吸道疾病之一，儿童哮喘发作常表现为咳嗽和喘鸣，多数家长往往不能正确区分儿童的哮喘与上呼吸道感染、感冒，由于未给予重视，导致病情加重[1-3]。根据流行病学调查研究结果，2010 年我国 33 个城市 0-14 岁人群哮喘患病率要高于 2000 年，且根据全球哮喘防治委员会（GINA）报告，全球患有哮喘的人群中，儿童哮喘的患病率上升明显，说明儿童哮喘不仅在我国，乃至在全球范围内也是一个较为严重的公共卫生问题[4-6]。随着临床对支气管哮喘发病机制的不断深入，研究者开始提出一些新的儿童哮喘辅助诊断方法，目前有研究指出将呼出气冷凝液、呼出气一氧化氮（Fractional exhaled nitric oxide，FeNO）及尿液代谢相关指标作为儿童哮喘的辅助诊断指标[7-9]。机体内 FeNO 主要由上皮细胞和巨噬细胞产生，相关报道指出上述两种细胞与哮喘的发病机制密切相关[10-12]。目前临床中对儿童哮喘的研究年龄范围多为 3-16 岁之间，而本研究将 3 岁或以下哮喘患儿与毛细支气管炎患儿的 FeNO 浓度进行比较，同时对 FeNO 与哮喘患儿病情的相关性进行探讨，为临床中哮喘患儿的诊断提供一定的理论依据。

1 资料与方法

1.1 临床资料

选择 2017 年 1 月至 2018 年 1 月期间于我院确诊为哮喘的患儿 60 例作为哮喘组，纳入标准：① 年龄≤ 3 岁；② 支气管哮喘的诊断符合中华医学会制定的《儿童支气管哮喘诊断和防治指南》（2016 年版）[13]。排除标准：① 患有早产史的患儿；② 呼吸系统畸形患儿；③ 伴有心肝肾等重大脏器疾病的患儿。同时选取我院收治的毛细支气管炎患儿 60 例作为毛细支气管炎组，纳入标准：① 临床呈现鼻部卡他症状、阵发性咳嗽，38-39℃的中等度发热，其他可见呕吐、易激怒、喂养量下降；② 常见感染病原体（如呼吸道合胞病毒）感染阳性；③ X 线表现肺部过度充气征或斑片状浸润阴影。排除标准：① 合并肺源性心脏疾病患儿；② 先天性心脏疾病患儿；③ 血流动力学异常、肺部先天畸形、肝肾重大脏器疾病的患儿。并选取我院同期健康儿童 40 例作为对照组。哮喘组患儿男 36 例，女 24 例，年龄 1-3 岁，平均（2.11± 0.80）岁，体重 8.3-15.8 Kg，平均体重为（13.26± 2.32）Kg。毛细支气管炎组男 34 例，女 26 例，年龄 1-3 岁，平均（1.90± 0.72）岁，体重 8.4-15.6 Kg，平均体重为（12.62± 2.45）Kg。对照组男 25 例，女 15 例，年龄 1-3 岁，平均（2.15± 0.73）岁，体重 8.5-15.9 Kg，平均体重为（12.55± 2.81）Kg。三组儿童的性别比例、年龄、体重等基本资料经比较无统计学差异（P>0.05），具有可比性。将 60 例哮喘组患儿在治疗 4 周后根据不同的病情控制情况分组，分为哮喘控制组（23 例）、哮喘部分控制组（19 例）与哮喘未控制组（18 例），分组标准为[6,7]：① 哮喘控制，无日间症状或日间症状的发生频率为≤ 2 天 / 周，无夜间憋醒，无应激缓解用药，无活动受限；② 哮喘部分控制，1 周内出现以下 1 项特征：＞2 天或≤ 2 天但多次出现日间症状，有夜间憋醒，＞2 次 / 周使用应激药物，存在活动受限，肺功能小于正常预测值或本人最佳值的 80%；③ 哮喘未控制：1 周内出现以下 3 项以上特征：＞2 天或≤ 2 天但多次出现日间症状，有夜间憋醒，＞2 次 / 周使用应激药物，存在活动受限，肺功能小于正常预测值或本人最佳值的 80%；根据不同的患儿哮喘亚型将哮喘患儿分为咳嗽变异性组 23 例与非咳嗽变异性组 37 例，咳嗽变异性哮喘的诊断符合中华医学会制定的《儿童支气管哮喘诊断和防治指南》（2016 年版）[13]诊断标准。本研究经我院伦理委员会批准予以进行。

1.2 研究方法

哮喘患儿给予吸氧、平喘、祛痰、抗过敏、抗生素等治疗，毛细支气管炎患儿给予控制感染、止咳祛痰、解痉平喘等治疗。本研究中 FeNO 的测定采用无锡尚沃生物科技有限公司提供的纳库仑一氧化氮分析仪，呼气方法选择潮气呼吸模式，在患儿平静呼吸状态下用面罩扣住口鼻，采集气体样本；如果患儿安静，无哭闹，潮气呼吸法可不给予药物镇静。FeNO 的单位用 ppb（parts per billion）表示，1ppb=1 ug/g[14]。哮喘组与毛细支气管炎组在治疗前、治疗后 1 h、治疗 4 周后进行 FeNO 的浓度测定，对照组在体检时进行 FeNO 的浓度测定。

1.3 观察指标

比较对照组体检时、哮喘组及毛细支气管炎组不同治疗期间的 FeNO 浓度，并比较不同病情控制程度和哮喘亚型患儿的 FeNO 浓度，并分析哮喘患儿 FeNO 浓度与病情控制的相关性。

1.4 统计学方法

采用 SPSS 21.0 软件对数据进行统计学分析，计量资料采用均值± 标准差（$\bar{x}\pm s$）形式表示，组间两两比较采用 t 检验，多组间比较采用 F 检验，计数资料采用率或者例的形式表示，采用 χ^2 检验。相关性分析采用 Pearson 法进行分析，以 P<0.05 表示差异具有统计学意义。

2 结果

2.1 哮喘组、毛细支气管炎组、对照组 FeNO 浓度比较

哮喘组治疗前的 FeNO 浓度高于毛细支气管炎组治疗前和对照组体检时的 FeNO 浓度（t=8.741、16.895，P=0.000、0.000）；与治疗前和治疗后 1 h 比较，治疗 4 周后哮喘组与毛细支气管炎组患儿 FeNO 浓度降低（P<0.05），而治疗后 1 h 哮喘组与毛细支气管炎组患儿 FeNO 浓度与治疗前比较差异无统计学意义（P>0.05）；治疗后 1 h 及治疗 4 周后哮喘组 FeNO 浓度均高于毛细支气管炎组（P<0.05），见表 1。

2.2 不同病情控制和哮喘亚型患儿 FeNO 浓度比较

哮喘控制组 FeNO 浓度低于哮喘部分控制组与哮喘未控制组，差异有统计学意义（t=3.128、4.184，P=0.017、0.000），哮喘部分控制组 FeNO 浓度低于哮喘未控制组，差异有统计学意义（t=3.182，P=0.000），咳嗽变异性组 FeNO 浓度高于非咳嗽变异性组，差异有统计学意义（t=2.532，P=0.014）。

2.3 哮喘患儿 FeNO 浓度与病情控制相关性分析

Pearson 相关性分析显示，哮喘患儿病情控制程度与 FeNO 浓度呈负相关，FeNO 浓度越低，病情控制程度越好（r= -0.512，P=0.034）。

3 讨论

儿童支气管哮喘是一种慢性的非特异性气道炎症，发病机制中存在多种免疫因子和炎症因子的参与，较为复杂[15-17]。毛细

表 1 三组 FeNO 浓度比较($\bar{x}\pm s$,ppb)

Table 1 Comparison of FeNO concentrations in three groups($\bar{x}\pm s$, ppb)

Groups	n	Before treatment/At the time of physical examination	1 h after treatment	4 weeks after treatment
Asthma group	60	16.72± 8.84	14.39± 9.06	12.73± 7.85*#
Bronchiolitis group	60	11.33± 6.62	10.90± 7.49	9.93± 5.31*#
Control group	40	8.32± 0.45	-	-
F/t	-	8.741	14.860	11.743
P	-	0.000	0.000	0.000

Note: Compared with before treatment, *P<0.05; compared with the beginning of treatment, #P<0.05.

表2 不同病情控制及哮喘亚型哮喘患儿 FeNO 浓度($\bar{x}\pm s$,ppb)

Table 2 The concentration of FeNO in infant with different disease control and asthma subtypes($\bar{x}\pm s$, ppb)

Groups		n	Concentration of FeNO
Disease control	Asthma controlled group	23	8.33± 0.28*#
	Asthma part controlled	19	14.12± 2.74#
	Asthma uncontrolled group	18	16.87± 2.81
Asthma subtypes	Cough variant group	23	8.41± 0.35&
	Non-cough variant group	37	15.47± 2.49

Note: Compared with asthma part controlled group, *P<0.05; compared with asthma uncontrolled group, #P<0.05; compared with non-cough variant group, &P<0.05.

支气管炎为儿童中多见、特有的呼吸道感染性疾病,多表现为小呼吸道阻塞、气促、憋喘、组织缺氧,该症多见于 2 岁以下的儿童,其与儿童哮喘鉴别主要在于毛细支气管炎的憋喘、气促为初次发病,而哮喘的憋喘、气促具有反复性[18-20]。目前临床诊断儿童哮喘的主要方式为肺功能,但针对 3 岁以下儿童,肺功能作为评价指标是不准确的,然而往往儿童哮喘在儿童阶段为初发,如果哮喘在儿童时期可以通过一定方法得到早期诊断且进行治疗,有助于减少儿童时期的哮喘发病率[21-23]。FeNO 为近几年临床研究的热点, 有研究对健康人群与哮喘人群的 FeNO 进行检测,结果发现哮喘人群的 FeNO 含量均高于 46ppb,认为成人 FeNO 含量高于 46ppb 可诊断为哮喘,对于儿童哮喘人群[24],有研究对学龄前儿童进行 FeNO 检测,认为 25ppb 对儿童哮喘的具有诊断意义[25]。

本研究将 3 岁或以下患有哮喘的儿童作为研究对象,分别对哮喘组、毛细支气管炎组及健康对照组的 FeNO 浓度进行测定,同时对哮喘患儿的病情控制与 FeNO 浓度的相关性进行分析。从本研究结果可以得到,治疗前哮喘组、毛细支气管炎组 FeNO 浓度高于对照组, 哮喘组不同治疗期间 FeNO 浓度高于毛细支气管炎组,差异均有统计学意义(P<0.05)。哮喘控制组患儿 FeNO 浓度低于哮喘部分控制组与哮喘未控制组(P<0.05),咳嗽变异性组 FeNO 浓度高于非咳嗽变异性组(P<0.05)。分析原因可能是哮喘患儿的嗜酸性粒细胞增多,而嗜酸性粒细胞能促进 FeNO 产生反应,炎症细胞分泌的细胞因子能促进上皮细胞诱导一,同时哮喘患儿体内都有一定程度的炎症氧化氮合成酶表达,从而进一步导致 FeNO 增加,咳嗽变异性引起的气道炎症较非咳嗽变异性更为严重,因此 FeNO 浓度更高[26-28]。通过相关性分析得到,FeNO 浓度与病情控制存在负相关性,FeNO 浓度越低,病情控制程度越好(P<0.05),FeNO 浓度越高表明气道炎症越严重,FeNO 浓度降低,说明支气管哮喘的炎症经治疗后逐步得到控制。Soto-Ramos M 等人[29,30]通过对哮喘患儿FeNO 浓度进行测定,研究得出低 FeNO 浓度的患儿较高 FeNO 浓度的患儿有较好的哮喘控制。本研究的不足之处在于纳入相关的儿童病例数较少,需要更多的临床样本进行验证分析。

综上所述,在哮喘患儿中 FeNO 浓度高于毛细支气管炎患儿、健康儿童,且 FeNO 与儿童哮喘的病情控制存在相关性,可作为儿童哮喘的辅助诊断指标,但仍需要更多的研究来验证。

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