·老年人呼吸系统疾病专栏·

重症哮喘表型及内型的研究进展

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【摘 要】 支气管哮喘(简称哮喘)是由多种炎症细胞及细胞组分参与的气道慢性炎症性疾病,目前它被认为是一种异质性疾病,尤其重症哮喘。根据发病机制、临床表现及生物标志物等对重症哮喘患者进行精准分型及个体化治疗是目前研究的热点,可使哮喘患者获得最佳控制,本文对重症哮喘表型及内型进行了综述。

【关键词】 哮喘;重症;表型;内型
【中图分类号】 R562.25 【文献标志码】 A 【DOI】 10.11915/j.issn.1671-5403.2017.03.039

Progress in the research of phenotypes and endotypes of severe asthma

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【Abstract】 Bronchial asthma (also called asthma) is a chronic airway inflammatory disease, with involvement of a variety of inflammatory cells and cellular components. Nowadays, asthma, and severe asthma in particular, is increasingly recognized as a heterogeneous disease. Based on its pathogenesis, clinical manifestations, biomarkers, and so on, precise classification and individualized treatment have become current research hotspot for severe asthma patients. Only in this way, these patients can be well-controlled. The article reviewed the phenotypes and endotypes of severe asthma.

【Key words】 asthma; severe; phenotype; endotype
This work was supported by the National Natural Science Foundation of China (11374370); *Major Equipment Development Project of Science and Technology Ministry* (2012YQ150092).

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哮喘近年被认为是一种异质性疾病[1],而重症哮喘是指在过去一年中≥50%的时间需要给予全球哮喘防治创议(global initiative for asthma,GINA)指南中4~5级哮喘药物治疗,即高剂量吸入激素联合长效β_2受体激动剂和(或)白三烯调节剂/缓释茶碱,或全身激素治疗才能维持哮喘控制状态或上述治疗下仍不能控制哮喘[2]。研究表明,约5%~10%的哮喘患者为重症哮喘患者[3]。重症哮喘反复发作会导致患者生活质量下降,不仅消耗大量医疗费用,而且使用大剂量糖皮质激素(简称激素)会导致激素相关并发症风险升高[3-5]。

表型(phenotype)通常指生物体由基因型和环境相互作用后而被观察到的特征[6,7]。内型(endotype)指通过一个特殊的可以识别的生物途径来解释表型中观察到的特性,即从发病机制层面反映哮喘的本质[7-9]。哮喘表型指通过哮喘患者的病史、临床特征、病理生理学等生物学特征以及对治疗的反应等鉴定出不同的哮喘亚型[10,11]。重症哮喘患者具有不同的表型和内型,其病理机制复杂多样[9]。重症哮喘不同表型的特征包括年龄、性别、发病年龄、特应性状态、肥胖、发作频率、阿司匹林加重性呼吸系统疾病(aspirin aggravated respiratory disease,AERD)及激素抵抗等。然而,这些特征同时存在大量重叠[5]。重症哮喘不同表型和内型的诊断及个体化治疗将有助于优化重症哮喘患者的管理,改善哮喘预后[12]。目前被广泛认可的重症哮喘表型不是很多,本文对7种不同的重症哮喘表型进行了综述。

收稿日期:2016-12-12;**修回日期**:2017-01-25
基金项目:国家自然科学基金(11374370);科技部重大仪器开发项目(2012YQ150092)
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1 与炎症生物标志物相关的重症哮喘表型

1.1 高辅助性 T 淋巴细胞 2(helper T cell 2,Th2)型哮喘/晚发型嗜酸性粒细胞型哮喘

高 Th2 型重症哮喘的发病机制与 Th2 炎症通路参与的气道炎症和气道重构有关。首先上皮细胞分泌白细胞介素 -25(interleukin-25,IL-25)和白细胞介素 -33(interleukin-33,IL-33)激活肺部树突状细胞,并诱导 CD^4 + T 淋巴细胞分化为 Th2,其次激活的 Th2 细胞可产生特定的细胞因子白细胞介素 -4(interleukin-4,IL-4)、IL-5I 和 L-13,参与 Th2 型炎症并促进 B 淋巴细胞合成免疫球蛋白 E(immunoglobulin,IgE)。此外,Th17 炎症通路也参与重症哮喘的发病过程[13]。重症哮喘研究项目(Severe Asthma Research Program,SARP)结果表明,大约 50% 重症哮喘与 Th2 型辅助性 T 淋巴细胞水平持续升高相关[14-17]。高 Th2 型重症哮喘患者的表型特征为患者临床症状更重、嗜酸性粒细胞增多、疾病多为早发型、患者存在过敏反应和 IgE 水平升高,以及 Th2 型炎症抑制剂有效[8,18,19]。高 Th2 型重症哮喘的炎症生物标志物包括嗜酸性粒细胞、高水平呼出气一氧化氮((fractional exhaled nitric oxide,FeNO)、骨膜蛋白、溴酪氨酸、嗜酸性粒细胞趋化因子。研究表明气道或痰液中嗜酸性粒细胞增多的患者对激素治疗可能更有效。

晚发型嗜酸性粒细胞型哮喘多见于成人,而儿童期哮喘发病常与过敏相关[5]。晚发型嗜酸性粒细胞型重症哮喘约占重症哮喘患者的 25%,患者血液和肺部嗜酸性粒细胞持续可见,临床症状更多,第一秒用力呼气量(forced expiratory volume in 1 second,FEV1)水平更低,FeNO 水平增高,过敏性因素较少,更易出现重症急性加重以及治疗困难等[5,20-23]。

1.2 中性粒细胞型哮喘

中性粒细胞型哮喘的致病原因目前尚不清楚,可能是吸烟、肥胖、空气污染、职业刺激性接触以及病毒、细菌感染等多因素导致中性粒细胞浸润型气道炎症[7]。一般哮喘患者诱导痰中的中性粒细胞比例 >(60% ~ 63%)定义为中性粒细胞型哮喘[24-26]。研究表明中性粒细胞型气道炎症可能与哮喘的持续性气流受限相关[23]。中性粒细胞型重症哮喘表型特征为老年人、吸烟,常见于接近致死性哮喘或多次气管插管病史、突发性致死性等重症哮喘患者,伴有睡眠障碍和胃食管返流疾病患者的鼻窦炎发病率增高,同时对激素抵抗[27-29]。此类患者的支气管活检、支气管肺泡灌洗液和诱导痰中,均可见到较多的中性粒细胞,并且大多数患者中性粒细胞增加数量与疾病严重程度相关,中性粒细胞型哮喘相关的炎症介质包括 IL-8、弹性蛋白酶、基质金属蛋白酶 -9(matrix metalloproteinase-9,MMP-9)、IL-17A、白细胞三烯 B4(leukotriene B4,LTB4)、粒细胞 - 巨噬细胞集落刺激因子(granulocyte-macrophage colony stimulating factor,GM-CSF)和肿瘤坏死因子 -α(tumor necrosis factor alpha,TNF-α)[27]。

2 儿童期过敏性哮喘

研究表明,儿童期过敏性哮喘,即早发型过敏性哮喘,约占所有重症哮喘患者的 40% ~ 50%[30],发病机制可能与 IgE 介导的免疫反应有关。其表型特征包括儿童期发病、具有严重过敏史和哮喘家族史、总 IgE 水平升高。特征性生物标志物包括特异性 IgE 水平增高、高水平的 FeNO、半乳糖凝集素 -3、嗜酸性粒细胞增多。

3 成人期过敏性哮喘

成人期重度过敏性哮喘患者(34%)比成人期轻至中度持续性过敏性哮喘(52%)更少见[31]。重症成人期过敏性哮喘患者,通常在儿童期即患有过敏性鼻炎,成年后出现过敏性哮喘。早期识别此型患者的特应性及过敏原,对选择治疗及改善居住环境具有意义。研究表明对于 IgE 水平升高以及多种过敏原阳性的重症成人期发作性过敏性哮喘患者,使用奥马珠单抗治疗可减少哮喘急性发作频率及吸入激素的量[32,33]。

4 成人期非过敏性哮喘

成人期非过敏性哮喘患者在症状发作前多有病毒感染史、职业暴露史或服用阿司匹林,而儿童期哮喘患者较少有此类病史。相比早发型过敏型哮喘,12 岁之后患哮喘患者的特异性过敏症状或过敏皮肤测试阳性较少。因此,成人期非过敏性哮喘混杂因素很多,过敏性因素可能更难明确。

5 阿司匹林加重性呼吸系统疾病

阿司匹林加重性呼吸系统疾病(aspirin-exacerbated respiratory disease,AERD)包括哮喘、慢性鼻 - 鼻窦炎(chronic rhinosinusitis,CRS)、鼻息肉以及摄入阿司匹林和其他抑制环氧合酶 -1 的非甾体类抗炎药(non steroidal anti-inflammatory drugs,NSAID)后出现的急性上、下呼吸道反应。AERD 是

多种重症哮喘表型复杂重叠的表现。约50%的AERD患者外周血嗜酸性粒细胞增多。研究表明，30%～70%的AERD患者是特应性体质患者[5]。

6 哮喘性肉芽肿

一些重症哮喘患者进行肺组织活检时被发现存在肉芽肿性炎症，例如，变应性肉芽肿血管炎（churg-strauss syndrome，CSS）、过敏性支气管肺曲霉病（allergic broncho-pulmonary aspergillosis，ABPA）等。大多数哮喘性肉芽肿患者的外周血嗜酸性粒细胞增多，FeNO水平升高，部分患者出现过敏症状[34]。

7 与临床特征相关的重症哮喘表型

7.1 激素抵抗型哮喘

部分哮喘患者长期或大量使用激素治疗后疗效仍不理想，这部分对激素治疗不敏感的哮喘称为激素抵抗型哮喘，约占哮喘总患病率的5%～10%，具有高龄、病史长、急诊就诊及住院率高、严重的气道高反应、易出现夜间喘息、诱导痰中中性粒细胞增多等特点。其发病机制较为复杂，可能与糖皮质激素受体异常、遗传基因以及免疫调节等机制有关。

7.2 频繁发作型哮喘

频繁发作型哮喘尚无一致的定义，一般指哮喘发作1年超过2或3次[2]，重症哮喘患者约30%符合频繁发作的定义[35]。频繁发作型哮喘患者具有更高的外周气道阻力、外周血和支气管肺泡灌洗液中嗜酸性粒细胞持续增多。此外，共存疾病更多，如慢性鼻窦炎、反复发生的呼吸道感染、吸烟、肥胖、阻塞性睡眠呼吸暂停及心理社会问题等[36-38]。

7.3 肥胖型哮喘

2014年GINA指南中首次提出肥胖型哮喘[39]。肥胖型哮喘患者体质量指数（body mass index，BMI）≥30 kg/m^2、女性居多、中度气道高反应性（airway hyper-reactivity，AHR）及可逆性、哮喘症状重、气道重塑发生早、哮喘晚期激素治疗效果较差、诱导痰嗜酸性粒细胞数量低而中性粒细胞数量高、特应性低（IgE水平不高）、对激素药物反应不佳等。一项荷兰队列研究表明，重症哮喘队列中肥胖型哮喘的发生率为21%[40]；英国一项队列研究表明，肥胖型哮喘的发生率为48%[41]。肥胖型哮喘常难控制，并且对传统哮喘治疗药物反应差。研究表明，肥胖型哮喘患者血清中IL-6、TNF-α及瘦素水平升高，而脂联素水平下降[42]。

7.4 围绝经期哮喘

围绝经期哮喘是指女性末次月经后1年内发生的哮喘[43,44]，发病机制可能是围绝经期女性激素水平降低，导致气道免疫炎症反应增强[45]。研究表明绝经期哮喘患者诱导痰中的中性粒细胞比例较高，而嗜酸性粒细胞比例轻度降低[44]。此外，绝经期发病的哮喘患者特应性低，相比单纯哮喘患者，呼吸困难症状明显，存在焦虑比例高，哮喘常规治疗效果差[44,46]。

综上所述，重症哮喘存在明显的异质性，未来研究方向应从重症哮喘的临床表型逐步转向分子表型，开展对不同表型重症哮喘的临床特征、生物标志物及个体治疗的研究将有助于控制哮喘，使更多哮喘患者从中获益。目前重症哮喘表型及内型更深层次的机制仍未阐明，具体表型的分型方法尚需进一步研究。虽然对这些表型尚未达成共识，但可以肯定的是，表型及内型研究有助于重症哮喘患者的精准诊断、科学管理以及有效个体治疗方案的制定。

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(编辑:王彩霞)