呼吸病学组

ANCA Contribute to Airway Inflammation via Induction of Neutrophil Extracellular Traps in Children with Bronchiolitis Obliterans

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Abstract

Objective: It was found that the level of ANCA in children with Bronchiolitis Obliterans (BO) was increased and was related to the severity of the disease. This study aims to explore the mechanism of ANCA in it.

Methods: The levels of NETs and inflammatory markers in children with BO were detected. ANCA IgG was extracted to stimulate polymorphonuclear (PMN) to co-culture with small airway epithelial cell (SAEC), and SAEC were also directly treated with Neutrophil Extracellular Traps (NETs). The production level of NETs and the level of inflammatory cytokines released by SAEC were detected.

Results: The levels of NETs and inflammatory factors including IL-1, IL-6, IL-8, IL-10 and IFN-γ in the blood of children with BO were significantly higher than those in the normal control group. ANCA IgG stimulated PMN to generate ROS and NETs. The co-culture of PMN stimulated by ANCA IgG with SAEC can significantly increase the expression of cytokines including TNF-α, IL-1, IL-8, IL-17, TGF-β1 and TIMP-1 in SAEC. NETs treated SAEC showed decreased cell viability and increased the expression of cytokines including TNF-α, IL-8, IL-17, TGF-β1 and TIMP-1.

Conclusion: ANCA may mediate airway inflammation by generating NETs in the development of BO in children.

Respiratory infections in X-linked hyper-IgM syndrome with CD40LG mutation: A case series of seven children in China

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Abstract

Background: X-linked hyper-immunoglobulin M (XHIGM), a primary immunodeficiency syndrome caused by mutations in the CD40 ligand gene, presents with recurrent respiratory infections in pediatric patients. We aimed to evaluate the spectrum of clinical features and respiratory pathogens in pediatric patients with XHIGM in China.

Methods: We retrospectively reviewed seven pediatric patients who were diagnosed with XHIGM and received follow-up treatment at the Guangzhou Women and Children's Medical Center between January 2010 and January 2021. We determined their clinical characteristics, causative pathogens, and prognosis by performing peripheral immunological and genetic tests.

Results: The majority of respiratory infections in four of the seven patients were caused by *Talaromyces marneffei(T. marneffei)*. Two patients had viral infections caused by cytomegalovirus (CMV) and human adenovirus respectively. One patient had a mixed infection caused by *Pneumocystis carinii* and CMV. Except for one child who died of respiratory failure, one patient received hematopoietic stem cell transplantation (HSCT) and recovered well, the other five patients survived with regular infusions of intravenous immunoglobulin (IVIg) during the follow-up period. Six patients had reduced antibody levels, especially IgG, IgA, and IgE levels. Increased serum IgM levels were detected in four cases, and three cases presented normal IgM levels at onset. All children were diagnosed with XHIGM with *CD40LG* variation. Three novel mutations were identified in the present study.

Conclusions: Our study suggests that respiratory infections usually begin within 2 years old and fungi and viruses are important pathogens causing respiratory infections in children with XHIGM. In endemic areas, *T. marneffei* are the common pathogen of respiratory tract infection in children with the disease.

Keywords: X-linked hyper-immunoglobulin M syndrome, respiratory infection, children, pathogen, mutation

RSV 感染对 Calu-3 细胞 TMEM16A 氯离子通道及粘蛋白 MUC5AC 的作用

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【摘 要】

目的：探讨呼吸道合胞病毒（RSV）感染 Calu-3 细胞后 TMEM16A 氯离子通道、黏蛋白 MUC5AC 及嘌呤受体 $P2X_4$ 表达和功能的改变，理清这三者在 RSV 感染黏液高分泌体系中所起的作用。

方法：（1）RSV 培养与滴度测定（2）构建 RSV 感染 Calu-3 细胞模型（3）RT-PCR 法鉴定细胞感染模型的成功构建（4）CCK-8 实验鉴定细胞活性（5）RT-PCR、Q-PCR、Western-blot、细胞免疫荧光及碘离子外排等方法检测化学药物干预及 RSV 感染对 Calu-3 细胞 TMEM16A、MUC5AC、$P2X_4$ 基因及蛋白表达和 TMEM16A 钙激活氯离子通道功能的影响。

结果：（1）RT-PCR 显示在 Calu-3 细胞内，TMEM16 家族中 TMEM16a、d、e、f、h、j、k mRNA 均有表达，其中 TMEM16F 表达量最高，而 TMEM16A 在 RSV 感染 96 hrs 后明显上调。（2）RSV 感染 Calu-3 细胞 96 hrs 后，Q-PCR 显示 TMEM16A、MUC5AC 及 $P2X_4$ 在 mRNA 水平表达均是上调的；蛋白免疫印迹和细胞免疫荧光结果显示 TMEM16A 及 MUC5AC 的蛋白表达水平也呈现上调。（3）RSV 感染 Calu-3 细胞 96 hrs 后，钙激活氯离子通道激动剂 ionomycin 刺激下的碘离子外排减少，提示 RSV 感染可以抑制 TMEM16A 钙激活氯离子通道的功能。（4）IL-4 或 CaCCinh-A01 处理均可以抑制 RSV 感染引起的 MUC5AC 高表达。同时 CaCCinh-A01 还能抑制 RSV 感染引起的 TMEM16A 高表达，并且使 RSV 感染后抑制的 TMEM16A 钙激活氯离子通道功能进一步下降。

结论：（1）RSV 感染可以通过以 Th2 类细胞因子为主等多种炎症因子来促进 Calu-3 细胞 TMEM16A、MUC5AC 及 $P2X_4$ 的表达，而增加的 TMEM16A 及 $P2X_4$ 又可能进一步促进 MUC5AC 的产生及分泌。(2)RSV 感染可以通过某种未知机制来抑制 Calu-3 细胞 TMEM16A 氯离子通道的功能使 Cl^- 分泌减少，而上调的 $P2X_4$ 又使 Na^+ 内流增加，从而使 ASL 的水合下降。（3）RSV 感染时 ASL 中 MUC5AC 等粘蛋白的高分泌及水合作用的下降，可能促使病理性粘液分泌及粘液栓形成，造成气道阻塞及气流受限，进而引起咳嗽咳痰、反复喘息及胸闷甚至呼吸困难等 RSV 感染常见的临床症状。（4）TMEM16A 抑制剂(如 CaCCinh-A01)可能通过抑制 TMEM16A 氯离子通道来抑制病毒的复制，进而对 RSV 感染引起的病理性粘液高分泌起到一定的干扰作用。（5）TMEM16A 及 $P2X_4$ 在 RSV 感染的病理性粘液高分泌体系中起重要作用，可能成为潜在的 RSV 感染治疗药物靶点，并且 TMEM16A 抑制剂在 RSV 感染的预防及治疗方面也有一定的作用。（6）我们的工作初步研究了 RSV 感染后呼吸道病理性粘液高分泌的体系及可能的相关机制，同时也为 RSV 感染后引起毛细支气管炎、哮喘，慢性阻塞性肺疾病及囊性纤维化肺疾病等寻找新的药物靶标提供了更多思路。

过敏性哮喘和/或过敏性鼻炎患儿标准化尘螨特异性皮下免疫治疗疗效的长期随访研究

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【摘 要】

目的：评估过敏性哮喘和/或过敏性鼻炎患儿进行标准化尘螨特异性皮下免疫治疗(SCIT)的疗效，并探讨疗效的影响因素。

方法：选取2015年4月至2017年12月在佛山市妇幼保健院儿科免疫治疗中心就诊的5~14岁对尘螨过敏的哮喘和/或过敏性鼻炎172例，对其进行尘螨特异性免疫治疗联合药物治疗。在治疗开始前、治疗1年、治疗2年、治疗3年、停止治疗后2年评估临床疗效。评估指标包括：哮喘症状评分、鼻炎症状评分、药物评分、病情改善自我评价。

结果：患儿哮喘症状评分由治疗前的 9.1 ± 2.1 显著减低为 1 年时的 1.2 ± 0.5，2 年时的 1.1 ± 0.4 ，3 年时的 0.8± 0.5，停止治疗2年后0（P＜0.05）。鼻炎症状评分由治疗前的 10.5 ± 2.1 显著减低为 1 年时的 3.2 ± 1.5，2 年时的 2.4 ± 1.4 和 3 年时的 1.0± 0.5（P＜0.05），停止治疗2年后1.0± 0.5（P＜0.05）。药物评分由治疗前的 2.7± 1.1 显著减低为 1 年时的 2.2 ± 0.1，2 年时的1.2 ± 0.1和 3 年时的0.2 ± 0.1（P＜0.05），停止治疗2年后的0.2 ± 0.1 。停止治疗2年后，病情自我评价明显改善率为90.70%（156/172）。停止治疗2年后，单纯哮喘组临床疗效好于合并鼻炎组（100% vs87.87%，P=0.07）。

结果：标准化SCIT治疗使哮喘和/或变应性鼻炎患儿的哮喘、鼻炎症状明显减轻，用药减少，在停止治疗的2年仍维持长期疗效。单纯哮喘患儿疗效优于合并过敏性鼻炎患儿。基线期症状评分及药物评分高的的患儿疗效更显著。

儿童慢性肾脏病患者合并睡眠呼吸暂停低通气综合征 30 例临床分析

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【摘 要】

目的：探讨慢性肾脏病（chronic kidney disease，CKD）患者合并睡眠呼吸暂停低通气综合征（Obstructive sleep apnea and hypopnea syndrome，OSAHS）的临床特点。OSAHS 是一种全身疾病，主要特征为睡眠时打鼾伴有呼吸暂停和（或）呼吸浅表、夜间反复发生低氧血症、高碳酸血症和睡眠结构紊乱，进而导致白天嗜睡及多脏器损害，严重影响患者的生活质量及生存期。OSAHS 在 CKD 患者中的发生率高于健康人。OSAHS 的存在致使 CKD 患者的生活质量下降，同时增加其并发症，特别是心血管疾病（cardiovascular disease，CVD）的发生率及患者的死亡率。CKD 合并 OSAHS 发病隐匿，易被人们忽视。本研究就我院 CKD 患者鼾症、OSAHS 的发病情况，探讨 CKD 合并 OSAHS 的临床特点。

方法：对 2018 年 6 月至 2022 年 6 月于我院确诊 CKD 合并 OSAHS 的 30 例患者进行调查，调查内容包括个人基本情况（年龄、身高、体重）、睡眠呼吸情况（打鼾、张口呼吸、夜间血氧饱和度下降情况）、心血管疾病情况（高血压）等相关资料。分析 CKD 病情程度与 OSAHS 发生率的关系；CKD 合并 OSAHS 的临床特点。

结果：1.一般资料：纳入研究对象 30 例，男性 21 例，女性 9 例，平均年龄 8.23（±3.31）岁，平均 BMI19.55（±4.61）kg/m^2。平均肾脏病病史为 25.17（±30）月，其中肾病综合征 18 例，狼疮肾 2 例，紫癜性肾病 3 例，IgA 肾病 4 例，多囊肾 1 例，后天性肾囊肿 1 例，ANCA 相关肾炎 1 例。CKD1 期者 22 例；CKD2 期者 3 例；CKD3 期者 2 例；CKD4 期者 0 例；CKD5 期者 3 例。2.CKD 合并 OSAHS 患儿鼾症的发生率为 70%（21 例/30 例），张口呼吸发生率为 26.67%（8 例/30 例），夜间低氧血症发生率为 73.3%{其中轻度，中度、重度发生率分别为 53.3%（16 例/30 例）、16.7%（5 例/30 例）、3.3%（1 例/30 例）}。3.OSAHS 发生率：轻度、中度、重度 OSAHS 发生率分别为 83.3%（25 例/30 例）、6.7%（2 例/30 例）、10%（3 例/30 例）。各期 CKD 患者 OSAHS

病情分度分别为：CKD1 期{其轻度、中度、重度 OSAHS 发生率分别为 95.5%（21 例/22 例）、4.5%（1 例/22 例）、0%（0 例/22 例）}；CKD2 期{其轻度、中度、重度 OSAHS 发生率分别为 33.3%（1 例/3 例）、33.3%（1 例/3 例）、33.3%（1 例/3 例）}；CKD3 期{其轻度、中度、重度 OSAHS 发生率分别为 50%（1 例/2 例）、0%（0 例/2 例）、50%（1 例/2 例）}；CKD5 期{其轻度、中度、重度分别为 66.7%（2 例/3 例）、0%(0 例/3 例）、33.3%（1 例/3 例）}。4.CKD 患者病情程度与 OSAHS 病情程度的相关性：CKD 分期和 OSAHS 病情程度呈线性关系，随着 CKD 分期的增加，OSAHS 病情程度逐渐加重（P＜0.05）。5.患者的肾小球滤过率跟血 CO2 有显著相关性，随着血 CO2 的降低，肾小球滤过率随之降低。6.CKD 合并 OSAHS 者 CVD 的患病率为 46.67%（14 例/30 例）。

结论：1.本研究中 CKD 合并 OSAHS 以轻度 OSAHS 为主。2.随着 CKD 分期的增加，OSAHS 病情程度逐渐加重，控制 CKD 的进展可能有助于改善 OSAHS 病情。3.CKD 合并 OSAHS 的临床表现以打鼾、张口呼吸为主，可以作为筛查的临床判断标准。

关键词：慢性肾脏病；睡眠呼吸暂停低通气综合征；心血管疾病；睡眠呼吸暂停/低通气指数；

Age-dependent Clinical Characteristics in Young Children Hospitalized With Respiratory Syncytial Virus Infection

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Abstract

Background：Human Respiratory Syncytial Virus (HRSV) is the commonest cause of acute lower respiratory infections (LRIs) in children, The main clinical manifestation is fever, cough, wheezing, retractions,The age-dependent clinical characteristics remains to be defined, we investigated whether there were any age-related differences in clinic manifestations of LRTs casused by HRSV.

Methods： We enrolled 130 hospitalized children with LRTS caused by HRSV, who were stratified into four age groups,The percentages of main symptoms and signs were compared between the four age groups.

Results： The incidence of pneumonia was the same between the four age groups , patients of ≤ 6 months old less frequently experienced fever and the highest body temperature of ≥ 38.5℃ compared with other age groups,fever frequency increased with age, ＞12 months age groups less frequently experienced wheezing, tachypnoea ,hypoxia and retractions compared with ≤ 6 months old group.

Conclusions： There were age-related differences in clinic manifestations of LRTs casused by HRSV, Including fever lowers the sensitivity for RSV case detection among young children hospitalized with an LRTS,while the inclusion of wheezing, tachypnoea, retractions to identify a suspect case in ＞12months old patient may lowers the sensitivity to detect cases in the HRSV season.

Keywords： Human Respiratory Syncytial Virus; lower respiratory infections; clinical manifestation; hospitalized children.

Effect of early intervention of food allergy in infants on the occurrence of allergic diseases

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Abstract

Objective： The aim of this study was to investigate the potential influence of early intervention of food allergy in infants on the occurrence of allergic diseases.

Methods： A prospective study design was adopted in the study and data were collected from 5,712 neonates born in our hospital between January 2017 and October 2017. As of October 2018, a total of 274 infants with food allergy were diagnosed. They were divided into three groups according to whether standard intervention was carried out and whether probiotics were added along with the intervention. Meanwhile, 187 infants without food allergies at the same period were selected as the control group. The incidence of allergic diseases was recorded at 6 and 12 months after enrollment, and the differences of peripheral blood Eosinophil count (EOS) percentage and TGF-β1 at 12 months were compared.

Results： 69 subjects were included in the group of standard intervention of food allergy with probiotic addition, 134 subjects were in the group of standard intervention without probiotic addition, 71 subjects were in the non-standard or non-intervention group, and 187 subjects were in the control group. There was no significant difference in age, gender and family environment among the four groups (P> 0.05). After 6 and 12 months of follow-up, the incidence of eczema, wheezing or persistent cough and asthma in the past half year were different among the four groups, and the incidence in the non-standard or non-intervention group was significantly higher than that in the control group (P< 0.05). After 6 months of follow-up, there was no significant difference in the incidence of allergic rhinitis among the four groups (P> 0.05); but after 12 months of follow-up, the incidence of allergic rhinitis in the non-standard or non-intervention group was significantly higher than that in the control group (P< 0.05). After 12 months of follow-up, the differences of peripheral blood EOS percentage and TGF-β1 were significantly different in the four groups.

Specifically, these indexes in the non-standard or non-intervention group were significantly higher than those in the control group (P< 0.05), while these indexes in the groups of standard intervention of food allergy with or without probiotics addition were higher than those in the control group but lower than those in the non-standard or non-intervention group (P< 0.05)

Conclusion：Early intervention of food allergy in infants could reduce the incidence of allergic diseases. Therefore, comprehensive prevention and treatment measures including the addition of probiotics should be actively adopted to block the process of allergic diseases in infants with food allergy.

Keywords: Infant; food allergy; dietary intervention; allergic disease; follow-up

支气管舒张试验在哮喘诊治中的价值探讨

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【摘 要】

目的：支气管舒张试验是发现哮喘患者气流受限可逆程度的手段之一，但不同年龄段儿童适宜不同肺功能检测手段，相应的支气管舒张试验阳性界值不同于成人，故本文就支气管舒张试验在哮喘诊治中的价进行综述。

方法：总结基于多种肺功能检测方法的支气管舒张试验阳性界值，如肺量计、脉冲振荡、体容积描计仪等。评价体位对舒张试验结果的影响。回顾支气管舒张试验在哮喘治疗、监测中的应用及其与气道炎症的关系。

结果：基于肺量计的支气管舒张试验 FEV_1 改善率可能低于成人标准，其他评价指标也可用于哮喘的诊断。基于脉冲振荡、潮气分析及体描法的支气管舒张试验也具有发现气道可逆性的价值，另外需注意舒张试验时体位对于肺功能结果的影响。支气管舒张试验在哮喘的控制及未来风险预测中起到了重要提示作用。支气管舒张试验联合 FeNO 可以更加准确的预测哮喘未来风险。

结论：支气管舒张试验在哮喘的诊断和鉴别诊断中发挥着重要作用，同时亦可作为哮喘监测、未来风险评估以及预测 ICS 治疗反应的手段。针对儿童的特殊性，未来还需要不断探索更加适合不同年龄段儿童的肺功能检测方法以及相应的舒张试验阳性界值，并对多种肺功能检查手段联合应用的诊断及监测能力进行综合分析研究。