论著·临床研究

学龄前儿童反复喘息的相关危险因素分析

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［摘要］**目的·**探讨学龄前儿童反复喘息的相关危险因素。**方法·**选取2019年12月—2020年12月因喘息在上海市某儿童专科医院呼吸科住院诊治的学龄前儿童（年龄3~6岁）作为研究对象，随访12个月。根据喘息发作次数分偶发喘息组（1~2次/年）和反复喘息组（≥3次/年）。采用面对面问卷形式向患儿父母询问患儿基本情况、相关病史及潜在的危险因素，包括儿童的年龄、性别、胎龄、低出生体质量史、湿疹史、变应性鼻炎史、食物过敏史、吸入花粉过敏史、毛细支气管炎病史、母亲生产年龄、生产方式、喂养方式、父母哮喘病史、生活区域（城市/农村）、被动吸烟史、宠物接触史、季节因素等。单因素分析比较2组学龄前儿童喘息发作的相关因素，Logistic回归分析反复喘息的独立危险因素。**结果·**共纳入370例，其中偶发喘息组204例（55.14%），反复喘息组166例（44.86%）。与反复喘息显著相关的危险因素包括年龄（χ^2=36.608，*P*=0.000）、性别（χ^2=4.290，*P*=0.038）、湿疹史（χ^2=6.250，*P*=0.012）、变应性鼻炎史（χ^2=10.787，*P*=0.001）、吸入花粉过敏史（χ^2=8.868，*P*=0.003）、毛细支气管炎病史（χ^2=27.898，*P*=0.000）、胎龄（χ^2=5.141，*P*=0.023）、喂养方式（χ^2=4.316，*P*=0.038）、父母哮喘病史（χ^2=5.050，*P*=0.025）和生活区域（χ^2=31.013，*P*=0.000）。Logistic回归分析结果显示：变应性鼻炎史（*OR*=4.759，95%*CI* 1.665~13.603）、毛细支气管炎史（*OR*=12.113，95%*CI* 5.686~25.802）、早产（*OR*=3.092，95%*CI* 1.120~8.539）和居住在城市（*OR*=2.395，95%*CI* 1.326~4.324）是反复喘息的独立危险因素。**结论·**学龄前儿童反复喘息的独立危险因素包括变应性鼻炎史、毛细支气管炎史、早产和居住于城市。

［关键词］喘息；反复；危险因素；学龄前儿童

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Risk factors of recurrent wheezing in preschool children

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[Abstract] Objective·To investigate the potential risk factors of recurrent wheezing in preschool children. **Methods·**A case-control study was conducted in 370 children with wheezing admitted to the Department of Respiratory Medicine in a specialized hospital for children in Shanghai from December 2019 to December 2020. The children were preschool children aged 3–6 years. According to the frequency of wheezing, pediatric patients were divided into occasional wheezing group (1–2 attacks per year) and recurrent wheezing group (≥3 attacks per year). The face-to-face questionnaire was performed to the parents responding for basic information and recurrent wheezing risk factors including the children age, gender, gestational age, birth weight, history of eczema, history of allergic rhinitis, history of food allergy, history of inhalational pollen allergy, history of bronchiolitis, maternal age, production mode, feeding pattern, history of parental asthma, resident area (city/village), passive smoking, history of pet contact, seasonal factors, etc. Univariate analysis was used to compare risk factors of recurrent wheezing between the two groups. Logistic regression analysis was used to analyze the independent risk factors associated with recurrent wheezing. **Results·**Three hundred and seventy cases were enrolled, including 204 cases (55.14%) in the occasional wheezing group and 166 cases (44.86%) in the recurrent wheezing group. A total of 10 risk factors were determined for recurrent wheezing, which included children's age (χ^2=36.608, *P*=0.000), gender (χ^2=4.290, *P*=0.038), eczema (χ^2=6.250, *P*=0.012), allergic rhinitis (χ^2=10.787, *P*=0.001), inhaling pollen (χ^2=8.868, *P*=0.003), history of bronchiolitis (χ^2=27.898, *P*=0.000), gestational age (χ^2=5.141, *P*=0.023), feeding pattern (χ^2=4.316,

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P=0.038), parental asthma history (χ^2=5.050, *P*=0.025) and resident area (χ^2=31.013, *P*=0.000). The Logistic regression showed that allergic rhinitis (*OR*=4.759, 95%*CI* 1.665−13.603), bronchiolitis (*OR*=12.113, 95%*CI* 5.686−25.802), premature birth (*OR*=3.092, 95%*CI* 1.120−8.539) and living in city (*OR*=2.395, 95%*CI* 1.326−4.324) were the independent risk factors of recurrent wheezing. **Conclusion**·The independent risk factors for recurrent wheezing in preschoolers include allergic rhinitis, bronchiolitis, premature birth and living in city.

[Key words] wheezing; recurrent; risk factor; preschool child

喘息是儿童呼吸系统疾病最常见的症状，25%~30%的儿童在婴儿期会患1次喘息，3岁时发生率达40%，6岁时达60%[1]。喘息性疾病是指以喘息为主要症状的一组疾病，好发于学龄前儿童。喘息发作与遗传、围生期因素、感染和环境等因素有关，反复喘息发作又与哮喘发生有密切关系[2-3]。由于空气污染等因素，哮喘的发病率在全球范围内一直呈上升趋势[4]。全国儿科哮喘协作组发现，我国0~14岁儿童哮喘患病率从1990年的0.91%上升至2010年的3.02%，超50%哮喘的发病始于学龄前，其中近1/3患儿未得到及时和准确的诊断[5-6]。由于症状和危险因素随时间变化，及时干预喘息危险因素可能会阻止哮喘的发生[7-8]。因此，学龄前儿童反复喘息的危险因素已经成为国内外研究者的关注点。本研究通过问卷调查及出院后随访12个月，分析学龄前儿童反复喘息的危险因素，为临床针对学龄前儿童反复喘息的干预研究提供依据。

1 对象与方法

1.1 研究对象、随访及分组

选取2019年12月—2020年12月上海市某儿童专科医院呼吸科因喘息住院诊治的患儿370例作为研究对象。患儿为学龄前儿童（年龄3~6岁），具有咳嗽、喘息、气急或胸闷症状，肺部可闻及散在或弥漫性喘鸣音，分别诊断为毛细支气管炎、喘息样支气管炎、喘息型支气管肺炎[9]。患者既往没有被诊断为婴幼儿喘息或哮喘；除外其他疾病引起的咳嗽、喘息、气急或胸闷，如支气管异物、支气管肺发育不良、先天性心脏病、纵隔肿物、胃食管反流等。

出院后，通过门诊或电话每3个月对患儿的喘息情况进行4次随访，共随访12个月。根据近1年喘息发作次数分为偶发喘息组204例（1~2次/年），反复喘息组166例（≥3次/年）[10]。

1.2 调查工具及资料收集

调查工具由研究团队自行设计。通过文献研究[5,11-12]、向5位呼吸内科专家行前期咨询并开展预调查，第一次专家测得所有条目的内容效度平均值为0.91；问卷修改后，第二次专家测得所有条目的内容效度平均值为0.95，重测信度为0.824。

采集所有儿童及其父母的有关资料，包括儿童的年龄、性别、胎龄、低出生体质量史、湿疹史、变应性鼻炎史、食物过敏史（牛奶、鸡蛋、海鲜）、吸入花粉过敏史、毛细支气管炎病史、母亲生产年龄、生产方式、喂养方式、父母哮喘病史、生活区域（居住城市/农村）、被动吸烟史、宠物接触史、季节因素。在问卷中备注说明“生活区域”中“城市”指人口密集、机动车较多的中心城区，“农村/城郊”指人口稀疏、机动车较少的地区[12]。被动吸烟是指不吸烟者每周有≥1次、每次≥15 min暴露于吸烟者呼出或燃烧香烟产生的烟雾中[13]。

共发放问卷390份，其中20份问卷未能填写完成而视为无效问卷，问卷回收率94.87%。

1.3 统计学方法

采用SPSS 25.0软件进行数据分析。将18项相关因素为自变量，患儿反复喘息或偶发喘息为因变量，分别赋值，采用χ^2检验进行比较，并根据分析结果，选出有统计学意义的变量行Logistic回归分析。*P*<0.05表示差异有统计学意义。

2 结果

2.1 一般资料

合计纳入370例，男251例（67.84%）、女119例（32.16%），中位年龄为50.0（44.0，60.1）个月，其中偶发喘息组204例（55.14%）、反复喘息组166例（44.86%）。各年龄段所占比例不同，差异有统计学

意义（P<0.05）；年龄较大的患儿，每年喘息发作次数较多（表1）。

2.2　单因素分析结果

与反复喘息显著相关的危险因素包括年龄（χ^2=36.608，P=0.000）、性别（χ^2=4.290，P=0.038）、湿疹史（χ^2=6.250，P=0.012）、变应性鼻炎史（χ^2=10.787，P=0.001）、吸入花粉过敏史（χ^2=8.868，P=0.003）、毛细支气管炎病史（χ^2=27.898，P=0.000）、胎龄（χ^2=5.141，P=0.023）、喂养方式（χ^2=4.316，P=0.038）、父母哮喘病史（χ^2=5.050，P=0.025）和生活区域（χ^2=31.013，P=0.000），见表1。

表1　反复喘息单因素分析［n（%）］

Tab 1　Univariate analysis of recurrent wheezing［n(%)］

Factor	State variable	Wheezing <3 times/year (n=204)	Wheezing ≥3 times/year (n=166)	χ^2 value	P value
Age/month	36–47	95 (46.6)	52 (31.3)	36.608	0.000
	48–59	86 (42.1)	51 (30.7)		
	60–72	23 (11.3)	63 (38.0)		
Gender	Male	129 (63.2)	122 (73.5)	4.290	0.038
	Female	75 (36.8)	44 (26.5)		
Resident area	Living in city	119 (58.3)	141 (84.9)	31.013	0.000
	Living in village	85 (41.7)	25 (15.1)		
Production mode	Cesarean	97 (47.5)	75 (45.2)	0.206	0.650
	Eutocia	107 (52.5)	91 (54.8)		
Gestational age	Premature delivery	7 (3.4)	15 (9.0)	5.141	0.023
	Term infant	197 (96.6)	151 (91.0)		
Feeding pattern	Artificial feeding /mixed feeding	120 (58.8)	115 (69.3)	4.316	0.038
	Breast feeding	84 (41.2)	51 (30.7)		
Suffocation	Yes	16 (7.8)	16 (9.6)	0.373	0.541
	No	188 (92.2)	150 (90.4)		
Birth weight	Low birth weight	27 (13.2)	25 (15.1)	0.252	0.615
	Normal birth weight	177 (86.8)	141 (84.9)		
Maternal age	≥35 years old	11 (5.4)	12 (7.2)	0.530	0.467
	<35 years old	193 (94.6)	154 (92.8)		
Parental asthma history	Yes	99 (48.5)	100 (60.2)	5.050	0.025
	No	105 (51.5)	66 (39.8)		
Eczema	Yes	140 (68.6)	133 (80.1)	6.250	0.012
	No	64 (31.4)	33 (19.9)		
Allergic rhinitis	Yes	111 (54.4)	118 (71.1)	10.787	0.001
	No	93 (45.6)	48 (28.9)		
Food allergy	Yes	106 (52.0)	127 (76.5)	3.401	0.065
	No	98 (48.0)	39 (23.5)		
Inhaling pollen	Yes	117 (57.4)	120 (72.3)	8.868	0.003
	No	87 (42.6)	46 (27.7)		
Bronchiolitis	Yes	60 (29.4)	94 (56.6)	27.898	0.000
	No	144 (70.6)	72 (43.4)		
Passive smoking	Yes	110 (53.9)	85 (51.2)	0.271	0.603
	No	94 (46.1)	81 (48.8)		
Pet contact	Yes	87 (42.6)	68 (41.0)	0.107	0.744
	No	117 (57.4)	98 (59.0)		
Seasonal factor	Winter and spring	110 (53.9)	79 (47.6)	1.468	0.226
	Summer and autumn	94 (46.1)	87 (52.4)		

2.3 Logistic回归分析结果

将单因素分析中有统计学意义的相关危险因素进行Logistic回归分析，结果显示：反复喘息的独立危险因素包括变应性鼻炎史（*OR*=4.759，95%*CI* 1.665~13.603）、毛细支气管炎史（*OR*=12.113，95%*CI* 5.686~25.802）、早产（*OR*=3.092，95%*CI* 1.120~8.539）和居住在城市（*OR*=2.395，95%*CI* 1.326~4.324），见表2。

表2 反复喘息的Logistic回归分析

Tab 2 Logistic regression analysis of recurrent wheezing

Variable	*β*	*Walds*	*P* value	*OR*	95%*CI*
Allergic rhinitis	1.560	8.476	0.004	4.759	1.665–13.603
Bronchiolitis	2.494	41.795	0.000	12.113	5.686–25.802
Premature birth	1.129	4.746	0.029	3.092	1.120–8.539
Urban residence	0.873	8.389	0.004	2.395	1.326–4.324

3 讨论

喘息是儿童哮喘的主要表现，喘息病因多样且有异质性，加之儿童呼吸系统的发育是一个动态变化的过程，每个阶段的影响因素可能会不同。本研究在对于喘息相关18项因素调查中，发现10项因素包括年龄、性别、湿疹史、变应性鼻炎史、吸入花粉过敏史、毛细支气管炎史、胎龄、喂养方式、父母哮喘史和生活区域，与学龄前儿童反复喘息密切相关。Logistic回归分析发现变应性鼻炎史、毛细支气管炎史、早产和居住在城市是学龄前儿童反复喘息的独立危险因素。反复喘息的患儿，其肺功能损害往往开始于学龄前期[14]。因此从喘息的患儿中识别出可能发展为哮喘的患儿，并进行早期有效干预，对于改善患儿的预后有重要意义[15-16]。

有研究[9,17]发现，学龄前儿童鼻炎与喘息的严重程度相关。随着鼻炎发作严重性/频率的增加，喘息发作次数也增加，中重度学龄前鼻炎患儿的喘息风险比没有鼻炎者高11倍，轻度鼻炎患儿的喘息风险也高出3倍以上，约25%的鼻炎患儿在晚发性喘息中影响更大。本组研究数据显示，变应性鼻炎史是学龄前儿童反复喘息的独立危险因素。喘息与特定的鼻炎表型有关，鼻涕最常见于喘息患儿，而鼻塞最常见于非喘息患儿。对有变应性鼻炎史的儿童，早期识别过敏原，避免接触过敏原引起鼻炎发作，有可能减少反复喘息发作的风险。

据报道[18-20]，婴幼儿毛细支气管炎后出现反复喘息的概率为30%~40%，且其中有31.8%可进展为哮喘；呼吸道合胞病毒和鼻病毒是毛细支气管炎中最常见的致病因素，两者都与反复喘息相关。本组研究显示毛细支气管炎史是反复喘息的独立危险因素，154例毛细支气管炎患儿学龄前发病后1年内出现喘息，其中≥3次/年喘息者94例（56.6%）。国外研究观察到早产可能与反复喘息有关，原因是早产儿肺部发育不成熟或早期机械通气导致肺部受损[21-22]。KOTECHA等[23]观察到早产儿患喘息在孕龄组中存在一定的风险梯度，与足月组相比，早产儿在8~9岁时肺功能值较低。我们的研究结果发现，早产儿相对于足月儿在学龄前期发生反复喘息的风险更大。因此，对于学龄前儿童，尤其是出生时为早产儿者，减少或避免反复呼吸道感染可减少反复喘息发作的风险。由于本研究纳入的是住院患儿，对于未住院的轻度反复喘息的患儿，可能会有不同的结论，仍需进一步研究。

居住环境可能与反复喘息有关。WHYAND等[24]发现暴露于NO_2且生活在靠近主要道路的地区与喘息性疾病发病率之间存在关联。也有学者发现，靠近交通车辆密度高的街道是复发性喘息和哮喘的危险因素（*OR*=1.79），而居住在“绿色区域”附近是保护因素（*OR*=0.50）[25]。一项涉及3~14岁儿童的流行病学调查发现：城区儿童喘息发生率（6.60%）明显高于乡镇儿童（3.20%）[26]。生命早期暴露于农场动物与过敏性疾病的发展呈负相关，农场动物似乎具有保护作用[27]。本研究观察到居住在城市增加反复喘息的风险，年龄较大的患儿每年喘息发作次数较多。年龄较大的患儿可能户外活动增多。在当前城市环境下，建议儿童外出时给予其防护措施，如戴防尘口罩等。重视城市环境改造，可能可以减轻儿童反复喘息发生的风险。

本研究存在不足。首先，研究对象是单中心呼吸科住院后随访患儿，病例代表性可能不足。其次，没有区分喘息发作的严重程度与高危因素暴露的关系，也没有检测与喘息高度相关的生物学标志。再次，本

研究的样本量不大，没有区分不同年龄患儿之间喘息的差别。

总之，本研究发现学龄前儿童反复喘息的独立危险因素包括变应性鼻炎史、毛细支气管炎史、早产和居住在城市环境等，提示对有高危因素的反复喘息的学龄前儿童，应注意规避上述危险因素，采取针对性预防策略。

利益冲突声明/Conflict of Interests

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All authors disclose no relevant conflict of interests.

伦理批准和知情同意/Ethics Approval and Patient Consent

本研究涉及的所有实验均已通过上海市儿童医院伦理委员会的审核批准（审批号2016R038-E01，2016R038-F02）。所有实验过程均遵照《Helsinki 标准/守则》的条例进行。受试对象或其亲属已经签署知情同意书。

The research protocol conducted in accordance with ethical guidelines of *Declaration of Helsinki* approved by Ethics Committee of Shanghai Children's Hospital （2016R038-E01, 2016R038-F02）. Consent letters have been signed by the research participants or their relatives.

作者贡献/Authors' Contributions

李爱求、董晓艳参与了研究方案的设计、论文的写作和修改，李爱求、张潇潇参与了数据分析，李爱求、姜允丽、肖艳赏、张潇潇、丁国栋、吴蓓蓉参与了数据采集、病例随访、研究实施。所有作者均阅读并同意了最终稿件的提交。
The study was designed by LI Aiqiu and DONG Xiaoyan. The manuscript was drafted and revised by LI Aiqiu and DONG Xiaoyan. The data was analyzed by LI Aiqiu and ZHANG Xiaoxiao. Data collection, case follow-up and study implementation was completed by LI Aiqiu, JIANG Yunli, XIAO Yanshang, ZHANG Xiaoxiao, DING Guodong and WU Beirong. All the authors have read the last version of paper and consented for submission.

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