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150 例川崎病患儿的冠脉受损的高危因素分析 *

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摘要 目的:分析与调查川崎病患儿的冠脉受损的高危因素,为改善患儿预后提供参考。**方法:**采用病例对照的方法,研究时间为 2016 年 8 月至 2019 年 4 月,选择 150 例在本院诊治的川崎病患儿,调查所有患者的流行病学状况并进行血液学检测。随访患儿的冠脉受损发生情况并进行高危因素调查与分析。**结果:**随访 6 个月,150 例川崎病患儿中继发冠脉受损 44 例,发生率为 29.3 %,作为病例组,106 例冠脉未受损的为对照组。两组一般资料对比无统计学意义(P>0.05)。两组入院时的白细胞计数、血小板计数、红细胞比容与血红蛋白值对比差异无统计学意义 (P>0.05)。病例组入院时的血清白介素 -1β (Interleukin-1β,IL-1β)、白介素 -6 (Interleukin-6,IL-6)、肿瘤坏死因子 -α(Tumor necrosis factor-α,TNF-α)值都显著高于对照组(P<0.05)。Logistic 回归方程分析显示 IL-1β、IL-6、TNF-α 都为导致冠脉受损发生的影响因素(P<0.05)。**结论:**川崎病继发冠脉受损比较常见,临床症状多表现为皮疹、球结膜充血、颈部淋巴结肿大、手足肿胀,IL-1β、IL-6、TNF-α 为导致冠脉受损发生的影响因素。

关键词:川崎病;冠脉受损;高危因素;白介素 -1β;肿瘤坏死因子 -α

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Analysis of High Risk Factors for Coronary Artery Damage in 150 Children with Kawereaki Disease*

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ABSTRACT Objective: To analysis and investigate the high-risk factors of coronary artery damage in children with Kawereaki disease, and to provide a reference for improving the prognosis of children. **Methods:** Used a case-control method, the study period were from August 2016 to April 2019. 150 cases of children with Kawereaki disease treated in our hospital were selected as the research objects. The epidemiological status of all cases were investigated and hematological tests were performed. Patients with coronary artery damage were followed up and the risk factors were investigated and analyzed. **Results:** During 6 months followed-up, there were 44 cases of coronary artery damage occurred in 150 cases of children with Kawereaki disease, the incidence rates were 29.3%. There were no significant differences in gender, age, and clinical symptoms between the two groups of children at admission (P>0.05). There were no significant differences in white blood cell counts, platelet counts, hematocrits, and hemoglobin values compared between the two groups of children at admission (P>0.05). The serum Interleukin-1β (IL-1β), Interleukin-6 (IL-6), Tumor necrosis factor-α (TNF-α) in the case group were significantly higher than those in the control group (P<0.05). Logistic regression equation analysis showed that IL-1β, IL-6 and TNF-α were all influencing factors leading to the occurrence of coronary artery damage (P<0.05). **Conclusion:** Kawereaki disease is more common with secondary coronary artery damage. Clinical symptoms are mostly rash, conjunctival hyperemia, cervical lymphadenopathy, and swelling of the hands and feet. IL-1β, IL-6, and TNF-α are the causes of coronary artery damage. Influencing factors.

Key words: Kawereaki disease; Coronary artery damage; High-risk factors; Interleukin-1β; Tumor necrosis factor-α

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前言

川崎病(Kawereaki disease,KD)是儿科常见的急性发热性出疹性疾病,也为一种好发于学龄前儿童的自身免疫性血管炎性疾病[1]。该病多发生于婴幼儿,80 %发生于 5 岁以内[2,3]。已有研究显示该病在一定的遗传易感性基础上,细菌、病毒感染以抗原或超抗原的形式引起机体的免疫激活, 特别是 T、B 淋巴细胞介导的细胞因子、免疫应答相互作用的级联放大效应在其中发挥了重要作用[4,5]。当前很多川崎病患儿伴随有冠脉受损,主要表现为全身中、小动脉急性非特异性血管炎,病变严重的

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可形成冠状动脉瘤[6,7]。未经治疗的川崎病患儿冠脉受损发生率高达 15 %-25 %,可影响患者的预后[8]。影像学为判断冠脉受损的主要方法,不过冠状动脉造影有一定的创伤性,且检查费用较高[9]。超声心动图具有方便、可重复、迅速、无创伤的特点,但是在显示冠状动脉分支远端时较为困难[10,11]。而早期进行川崎病患儿冠脉受损的危险因素调查,有利于冠脉受损的早期诊断和及时治疗,促进改善患儿的预后[12,13]。本文为此具体分析了川崎病患儿的冠脉受损的高危因素,现总结报道如下。

1 资料与方法

1.1 研究对象

采用病例对照的方法,研究时间为 2016 年 8 月至 2019 年 4 月,选择 150 例在本院诊治的川崎病患儿,纳入标准:年龄≤ 8 岁;本院伦理委员会批准了此次研究;符合川崎病的诊断标准(发热≥ 5 d,双侧眼球结膜充血,多形性皮疹,四肢末端改变,颈部淋巴结肿大);临床与随访资料完整。排除标准:临床与随访资料缺乏者;合并先天性心肝肾异常患儿。

1.2 研究方法

流行病学调查:登记患儿家长姓名、电话、工作单位、家庭住址、身份证号码、手机号码、患儿姓名、性别、年龄、发病日期、有无接触史、有无入托、幼儿园及早教机构名称及班级等。记录患者的临床表现与超声心动图表现。

血液标本检测:采集急性期(发病 0~3 d)静脉全血 3-5 mL,分离血清,将血清置于 -20℃以下冰箱中冷冻保存,一部分用于检测与扩增肠道病毒,为临床诊断提供实验室证据;另一部分备血用于细胞因子(IL-1β、IL-6、TNF-α)检测。同时记录患者的常规血液学指标,包括白细胞计数、血小板计数、红细胞比容、血红蛋白等。

1.3 随访调查

所有患儿随访 6 个月,6 个月内继发冠脉受损的患儿选入病例组,其余患儿归为对照组。

冠脉受损判断标准:所有患儿在随访中都给予超声心动图检查,患儿取左侧卧位,仔细、小心地旋转探头获得冠脉的满意图像。冠脉受损的诊断标:年龄 <5 岁,冠状动脉内径 >3 mm;年龄≥ 5 岁,冠状动脉内径 >4 mm。

1.4 统计方法

采用 SPSS20.0,计量数据采用($\bar{x}\pm s$)表示,对比为 t 检验;计数数据采用%表示,对比为 x^2 分析,影响因素分析采用多因素 Logistic 回归分析,检验水准为 α=0.05。

2 结果

2.1 预后情况

随访 6 个月,150 例川崎病患儿中继发冠脉受损 44 例,发生率为 29.3 %,作为病例组,106 例冠脉未受损的为对照组。两组一般资料对比无统计学意义(P>0.05)。见表 1。

表 1 两组一般资料对比

Table 1 Comparison of two groups of general information

Groups	n	Gender (male / female)	Age (years)	Clinlcal symptom (%)			
				Limb end change	Conjunctival congestion	Pleomorphic rash	Cervical lymphadenopathy
Case group	44	24/20	4.44±0.61	43(97.7)	27(61.4)	34(77.3)	22(50.0)
Control group	106	56/50	4.39±0.55	105(99.1)	60(56.6)	77(72.6)	53(50.0)

2.2 常规血液学指标对比

两组入院时的白细胞计数、血小板计数、红细胞比容与血红蛋白值对比无统计学意义(P>0.05)。见表 2。

表 2 两组常规血液学指标对比($\bar{x}\pm s$)

Table 2 Comparison of routine hematological indicators between two groups ($\bar{x}\pm s$)

Groups	n	Leucocyte count ($\times10^9$/L)	Platelet count ($\times10^9$/L)	Erythrocrit (g/L)	Hemoglobin (g/L)
Case group	44	16.55±2.15	401.44±56.39	0.36±0.06	112.76±15.68
Control group	106	17.01±2.52	398.72±54.10	0.35±0.05	114.27±12.01

2.3 细胞因子表达对比

病例组患儿入院时的血清 IL-1β、IL-6、TNF-α 值都显著高于对照组(P<0.05)。见表 3。

表 3 两组细胞因子表达对比(pg/mL,$\bar{x}\pm s$)

Table 3 Comparison of cytokine expression between the two groups (pg/mL, $\bar{x}\pm s$)

Groups	n	IL-1β	IL-6	TNF-α
Case group	44	79.48±14.58*	8.45±1.44*	239.58±42.49*
Control group	106	45.29±13.33	5.27±1.22	157.29±34.22

Note: Compared to the control group, *P<0.05.

2.4 影响因素分析

在 150 例患儿中，以是否继发冠脉受损作为因变量(0= 无，1= 有)，以单因素分析有统计学意义的 IL-1β、IL-6、TNF-α 等因素作为自变量，Logistic 回归方程分析显示 IL-1β、IL-6、TNF-α 都为导致冠脉受损发生的影响因素(P<0.05)。见表 4 与表 5。

表 4 川崎病继发冠脉受损的影响因素 Logistic 回归方程分析(n=150)

Table 4 Logistic regression equation analysis of influencing factors of coronary artery damage in Kawasaki disease (n=150)

Index	β	SE	P	OR	95%CI
IL-1β	0.766	0.280	0.006	2.151	1.242-3.723
IL-6	0.666	0.277	0.016	1.946	1.131-3.349
TNF-α	1.359	0.376	0.000	3.789	1.861-8.133

表 5 川崎病继发冠脉受损的影响因素赋值

Table 5 Evaluation of factors influencing secondary coronary artery damage to Kawasaki disease

Variable	Assignment standard
IL-1β	＞60 pg/mL=0，≤ 60 pg/mL=1
IL-6	＞7 pg/mL=0，≤ 7 pg/mL=1
TNF-α	＞210 pg/mL=0，≤ 210 pg/mL=1

3 讨论

川崎病的临床特征是持续发热、球结膜充血、不同程度的口腔黏膜炎、多形性皮疹、手足硬性肿胀伴指趾端膜状脱皮、非化脓性淋巴结炎[14]。主要病理改变是全身中小血管非特异性炎症，以冠脉受损最为严重，可形成冠脉扩张和冠脉瘤，甚至导致猝死[15]。但由于川崎病并发冠脉受损好发于近端，如果远端有病变，主干及分支近端也多受累，故该病的早期诊断率比较高。特别是超声心动图具有无痛、无创、可重复性强等特点，为该病早期诊断和治疗后动态随访的最佳方法之一[16,17]。

本研究显示随访 6 个月，150 例川崎病患儿中继发冠脉受损 44 例，发生率为 29.3 %。两组一般资料对比无统计学意义。当前也有研究认为川崎病引起的冠脉受损多出现在病程的 2-4 周，多数患儿在冠脉受损发病后 1-2 年内消失，但也有 5 %左右患儿遗留冠状动脉狭窄，发展为心肌梗死或猝死[18]。不过也有研究超声心动图在诊断近端的冠脉受损方面具有很高的敏感性与特异性，但对冠状动脉远端的冠脉受损，超声心动图的诊断敏感性较低[19,20]。

川崎病和冠脉受损的发生与发展具有一系列共性，其中包括：小于 5 岁儿童发病率高、有季节性和地域性、如果不能早期诊断、早期治疗，会导致严重并发症，甚至危害到患儿生命[21,22]。有研究表明两种疾病间存在内在联系，有许多川崎病合并或继发冠脉受损的病例报道。本研究显示两组患儿入院时的白细胞计数、血小板计数、红细胞比容与血红蛋白值对比差异无统计学意义，表明常规指标检测很难预测冠脉受损的发生。在冠脉受损的患儿中，多数表现为单纯左冠状动脉扩张或左右冠状动脉均扩张，单纯右冠状动脉扩张少见[23,24]。

川崎病的发生与机体免疫功能受抑制有关，尤其是细胞免疫在机体免疫应答中具有非常重要的作用。此外，细胞因子作为促炎因子和抗炎因子在川崎病的发生和发展中也起到重要作用[25]。已有研究表明多种促炎症因子与川崎病及并发症的发生有关[26]；同时冠脉受损患儿也可表现为促炎症因子表达升高。本研究显示病例组患儿入院时的血清 IL-1β、IL-6、TNF-α 值都显著高于对照组；Logistic 回归方程分析显示 IL-1β、IL-6、TNF-α 都为导致川崎病发生的影响因素。IL-1β 可介导炎症细胞浸润，加重炎症反应及诱导细胞凋亡，是细胞功能永久丧失的重要原因；IL-1β 能在神经系统中产生，并参与神经源性脑水肿的发生[27,28]。IL-6、TNF-α 可激活 JAK2/STAT3 信号系统，减弱肌质网功能，可刺激促纤维化因子表达，使组织纤维化，产生负性肌力作用[29]。特别是促炎症因子的过量释放可破坏成纤维细胞，影响冠脉病变修复，促发冠脉受损，并可使血小板聚集[30]。本研究也有一定的不足，纳入调查的因素比较少，且随访时间短，可能在影响因素分析上存在偏倚，将在后续分析中深入研究。

总之，川崎病继发冠脉受损比较常见，临床症状多表现为皮疹、球结膜充血、颈部淋巴结肿大、手足肿胀，IL-1β、IL-6、TNF-α 为导致冠脉受损发生的影响因素。

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