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综述

新型冠状病毒感染流行背景下的儿童多系统炎症综合征

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［摘要］儿童多系统炎症综合征（multisystem inflammatory syndrome in children, MIS-C）是在严重急性呼吸综合征冠状病毒-2（severe acute respiratory syndrome coronavirus 2, SARS-CoV-2）暴发流行的背景下出现的一种多系统受累综合征。MIS-C的临床表现与川崎病类似，但以发热及胃肠道症状为主要表现，严重者可出现中毒性休克和心功能不全。流行病学调查结果表明，大多数MIS-C患儿SARS-CoV-2抗体检测呈阳性。关于MIS-C的发病机制及病理生理过程尚不明确，SARS-CoV-2感染后的免疫失调被认为是主要原因。目前对于MIS-C的治疗以免疫球蛋白及对症支持治疗为主。该文对MIS-C的定义、流行病学、发病机制、临床表现、诊断、治疗及预后等进行了综述。

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［关键词］儿童多系统炎症综合征；新型冠状病毒感染；严重急性呼吸综合征冠状病毒2；儿童

Multisystem inflammatory syndrome in children in the context of coronavirus disease 2019 pandemic

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Abstract: Multisystem inflammatory syndrome in children (MIS-C) is a complex syndrome characterized by multi-organ involvement that has emerged in the context of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak. The clinical presentation of MIS-C is similar to Kawasaki disease but predominantly presents with fever and gastrointestinal symptoms, and severe cases can involve toxic shock and cardiac dysfunction. Epidemiological findings indicate that the majority of MIS-C patients test positive for SARS-CoV-2 antibodies. The pathogenesis and pathophysiology of MIS-C remain unclear, though immune dysregulation following SARS-CoV-2 infection is considered a major contributing factor. Current treatment approaches for MIS-C primarily involve intravenous immunoglobulin therapy and symptomatic supportive care. This review article provides a comprehensive overview of the definition, epidemiology, pathogenesis, clinical presentation, diagnosis, treatment, and prognosis of MIS-C.

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Key words: Multisystem inflammatory syndrome in children; Coronavirus disease 2019; Severe acute respiratory syndrome coronavirus 2; Child

2019年底一种由严重急性呼吸综合征冠状病毒-2（severe acute respiratory syndrome coronavirus 2, SARS-CoV-2）引起的新型冠状病毒感染（coronavirus disease 2019, COVID-19）暴发。此后的2年多，COVID-19迅速在全球蔓延，截至2022年11月，全球累计确诊人数已超过6.3亿，死亡人数高达658万，其中以欧美国家最严峻[1]。以往的流行病学调查表明，儿童和青少年感染COVID-19的病例较少，约为1.7%[2]，这可能与儿童生活环境单一、临床症状较轻，以及没有及时完善病原

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学检测有关。儿童确诊病例以呼吸道症状为主，预后良好[3]。但随着疫情的不断加剧，儿童病例不断增多，并出现类似川崎病（Kawasaki disease, KD）样，且以发热、消化道症状、心脏损害、休克等多器官损伤以及高炎症指标为主要特征的儿童重症病例，其最早在2020年4月由英国报道，随后在欧洲和美国等COVID-19高流行地区也报告了类似的病例[4-6]。研究表明，这些重症病例中约81%的患儿SARS-CoV-2 IgG呈阳性，而37%的患儿核酸呈阳性[7]。因此，2020年5月世界卫生组织（World Health Organization, WHO）将这种与COVID-19相关的儿童多系统炎症表现命名为儿童多系统炎症综合征（multisystem inflammatory syndrome in children, MIS-C）。本文对MIS-C的定义、流行病学、发病机制、临床表现、诊断、治疗及预后等进行了综述，以期提高临床医师对MIS-C的认识。

1 MIS-C的定义

多数MIS-C患儿病情危重，患病儿童中约80%的儿童因严重的KD样症状、休克及心脏功能障碍需收入重症监护病房治疗[8]。国际上关于MIS-C的诊断标准尚未统一，已有的初步诊断标准来自皇家儿科和儿童健康学院（Royal College of Pediatrics and Child Health, RCPCH）、美国疾病控制和预防中心（Centers for Disease Control and Prevention, CDC）和WHO。

1.1 RCPCH提出的MIS-C诊断标准

（1）发病年龄：所有年龄段；（2）临床症状：持续发热>38.5℃，存在单个或多个器官损害（胃肠道、呼吸、心脏、肾脏、神经系统）或休克；（3）实验室检查：C反应蛋白（C reactive protein, CRP）升高，中性粒细胞增多；（4）流行病学：SARS-CoV-2的反转录PCR呈阳性[9]。

1.2 美国CDC提出的MIS-C诊断标准

（1）发病年龄：年龄<21岁。（2）临床症状：体温>38.0℃且持续≥24 h或主观自觉发热≥24 h；存在≥2个器官/系统损害（胃肠道、呼吸、心脏、肾脏、血液、皮肤、神经系统）。（3）实验室检查：CRP、降钙素原（procalcitonin, PCT）、红细胞沉降率（erythrocyte sedimentation rate, ESR）、铁蛋白、白细胞介素-6等升高。（4）流行病学：近期有SARS-CoV-2感染，或症状出现前4周内有COVID-19暴露史[10]。

1.3 WHO提出的MIS-C诊断标准

（1）发病年龄：<19岁。（2）临床症状：持续3 d及以上的发热；至少有2种伴随症状，如皮疹或双侧非脓性结膜炎或黏液皮炎症状、低血压或休克、心血管功能障碍、腹泻、呕吐或腹痛。（3）实验室检查：ESR、CRP、PCT升高，凝血功能异常，心功能损伤。（4）流行病学：有SARS-CoV-2感染或COVID-19暴露史[11]。

尽管这些诊断标准不尽相同，但多系统功能障碍、高炎症反应指标及可疑或明确SARS-CoV-2感染的流行病学史是其共同点。

2 MIS-C的流行病学情况

由于MIS-C的临床表现与KD类似，因此早期被认为是KD的严重状态，但二者在流行病学方面存在明显不同。据统计，目前全球有9 000多例儿童被诊断为MIS-C，其中以美洲、欧洲、非洲、南亚和中东地区居多，病死率约0.8%[12-13]。荟萃分析显示，MIS-C儿童的平均年龄为9.3岁，其中男性占56.8%，并存在一定的种族差异性，以西班牙裔和黑人为主，分别为34.6%和31.5%[14]。MIS-C的发生与SARS-CoV-2感染是否有直接关系目前还不清楚，但多项大规模流行病学调查表明，MIS-C发病前2~6周有COVID-19感染或接触史[13, 15-16]，且实验室结果显示约81%的患儿SARS-CoV-2 IgG呈阳性，37%的患儿SARS-CoV-2核酸呈阳性[7]。因此MIS-C被认为与SARS-CoV-2感染关系密切。一项涉及美国26个州和纽约的MIS-C队列研究发现，肥胖患儿发生MIS-C的比例分别占37%和29%[17]，提示肥胖可能是MIS-C的一个危险因素。

KD是一种全身中小动脉性血管炎性病变，80%发生在5岁以下的儿童中，男性发病率高于女性[18]。KD最严重的并发症是引起冠状动脉病变和冠状动脉瘤，因此成为儿童获得性心脏病的主要原因[19]。KD的发病机制目前尚不明确，但与感染引起的自身免疫反应失调有关。

3 MIS-C的发病机制

流行病学调查表明，MIS-C的发病高峰时间往往较当地COVID-19发病高峰滞后4~5周，其延迟时间与获得性免疫应答时间相吻合。多项研究表明MIS-C可能是病毒感染后的异常免疫反应[17, 20-22]。因此，SARS-CoV-2感染后的异常免疫反应被认为是MIS-C的主要作用机制。机体感染SARS-CoV-2后，一方面通过诱导细胞凋亡减少病毒扩散，同时刺激辅助性T细胞分泌细胞因子，使

巨噬细胞、单核细胞、淋巴细胞活化，产生大量促炎细胞因子，如白细胞介素-1、白细胞介素-6、肿瘤坏死因子、铁蛋白等，起到清除病毒的作用，但不断增多的细胞因子在体内形成细胞因子风暴，引起全身炎症反应；同时病毒进入机体还可以激活B细胞，在浆细胞产生抗体，多种抗原抗体复合物作用于靶器官造成器官功能障碍[23-25]。研究发现，SARS-CoV-2能够侵入内皮细胞，导致内皮细胞损伤和血栓形成，从而造成器官功能障碍[26]，提示MIS-C的发病机制还可能与SARS-CoV-2感染导致血管内皮损伤有关。相关研究发现，与KD患儿相比，MIS-C患儿中的白细胞介素-6和白细胞介素-17A水平相对较低，提示这两种疾病之间的发病机制不同[27]。

4 MIS-C的临床表现及实验室检查

MIS-C患儿可出现多系统受累表现，根据主要临床表现的不同可分为3种类型。

（1）以持续发热和胃肠道症状为主，大多数患儿属于这一类。80%~99.4%的MIS-C患儿出现持续发热，多数患儿持续高热时间超过4 d，体温高于38℃；胃肠道症状的发生率为85.6%~90%，主要表现为腹痛、呕吐、腹泻等，严重时可出现类似急性阑尾炎、无菌性腹膜炎等急腹症表现，导致不必要的紧急手术[7, 28-29]。这些临床表现可能与MIS-C异常免疫反应导致大量炎症因子释放以及血管紧张素转化酶受体在胃肠道大量分布有关[30]。

（2）以休克和左心室功能障碍为主，发病率分别为74%和70%[7]。MIS-C患儿可能出现严重的心肌炎及血流动力学不稳定，在发生休克后对容量复苏效果差，往往需要使用血管活性药物，极少数情况下还需体外膜肺氧合治疗[31]。其损伤机制与SARS-CoV-2对心肌细胞的直接损伤以及严重的细胞因子风暴导致循环功能障碍有关[32]。

（3）KD样临床表现（结膜炎、淋巴结病、皮肤黏膜皮疹等）的发生率为17%[7, 28]。相关研究表明MIS-C患儿还可出现急性肾损害、肝损害和神经系统症状，但呼吸道症状少见[8, 17]。

MIS-C患儿处于高炎症反应状态，实验室检查常有炎症指标显著升高的表现。文献报道显示，92% MIS-C患儿至少有4种炎症指标升高[17]，包括CRP、ESR、中性粒细胞比例、降钙素原、铁蛋白、白细胞介素-6或白细胞介素-10等。除炎症指标升高外，还可出现淋巴细胞减少、血小板减少、低钠血症和低白蛋白血症等情况[33]。MIS-C患儿的白细胞、中性粒细胞、血小板计数和CRP水平通常比KD患儿更高，淋巴细胞减少和贫血更严重[34]。D-二聚体水平升高和纤维蛋白原水平降低通常提示有凝血功能异常，对MIS-C严重程度评估具有重要意义。研究表明，在MIS-C患儿中，N末端前体脑利钠肽和CRP水平显著升高可能提示左心室功能不全的发生，定期检查CRP和N末端前体脑利钠肽有助于识别MIS-C导致的心脏后遗症[33, 35]。在病原学检测中绝大多数MIS-C患儿SARS-CoV-2核酸检测为阴性，但抗体为阳性，提示MIS-C与SARS-CoV-2感染后的免疫性炎性反应有关[7, 34]。但是随着疫苗的广泛接种，尽管抗体检测可以区分先前的SARS-CoV-2感染和COVID-19疫苗接种，但其实用性和可用性存在局限性[36]。

5 MIS-C的治疗及远期影响

MIS-C是一种多系统受累的炎性综合征，需要多学科协助诊疗，治疗原则主要以支持、抗炎和器官功能支持治疗为主。美国风湿病学会针对MIS-C的诊疗制定了专门的临床指南，并不断进行更新[33, 37-38]。在最新的第3版临床指南中提出，静脉注射免疫球蛋白（intravenous immunoglobulin, IVIG）和低至中剂量糖皮质激素治疗是大多数MIS-C住院患儿的一线治疗[38]。建议IVIG使用量为2 g/kg（理想体重），最大总量不超过100 g。并要求在进行IVIG治疗之前，应先评估患儿的心功能及容量负荷。对于心功能低下或容量超负荷的患儿，建议IVIG分次给药，即每天1 g/kg，持续2 d，必要时加用利尿剂减轻心脏容量负荷。同时还因考虑到大剂量IVIG不仅有可能引起容量超负荷，同时还有诱发溶血性贫血的风险，故在病程中不推荐使用第2个疗程IVIG。低至中剂量糖皮质激素（每天1~2 mg/kg）可以与IVIG同时用于治疗，起到减轻炎症反应的作用。但在难治性MIS-C患儿中，建议使用大剂量糖皮质激素（每天10~30 mg/kg）冲击治疗，特别是对于需要大剂量或多种正性肌力药和/或血管加压药治疗的患儿。在初始免疫调节治疗后仍持续发热和/或有明显的终末器官受累的MIS-C被认为是难治性MIS-C，应及时进行强化治疗[39-41]。研究表明阿那白滞素或英夫利西单抗在难治性MIS-C的强化治疗过程中有重要意义[42]。

虽然MIS-C患儿临床症状多且病情重，往往需要在重症监护病房治疗，但其病死率低（约1.9%），一般经积极治疗后预后良好[28, 43]。多项研究发现，9%~24%的MIS-C患儿存在冠状动脉异

常，故对MIS-C患儿进行定期随访十分重要[3, 44]。

MIS-C是儿童感染SARS-CoV-2后的一种严重并发症，未及时有效治疗将影响患儿的生命健康，因此，提高对MIS-C早期识别与诊治能力对临床医师是十分重要的。

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