

·综述·

儿童烟雾病的临床概述

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基金项目
湖北省重点研发
计划(No. 2022B
CA027);
湖北省病理生理
学会基金(No. 20
21134);
同济医院自然科
学基金(No. 2020
JZKT651)
收稿日期
2022-03-29
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摘要 烟雾病是以颈内动脉末端慢性进行性闭塞为特征的临床疾病,随着疾病的进展,通常会导致患者发生缺血性或出血性卒中。它在东亚地区发病率较高,患者集中在儿童和成人两个年龄段,是一种相对常见的导致小儿卒中的病因。通过脑血管造影上特定的影像学表现,可以对烟雾病进行诊断,但尚缺乏有效的药物治疗去逆转或减缓疾病的进展,现阶段烟雾病的有效治疗手段是进行颅内血管重建手术,可以有效地降低患者发生脑卒中的风险。既往的研究多集中于探讨成人烟雾病的临床与治疗,儿童烟雾病在临床表现、治疗方案和围术期管理方面均和成人存在一些不同的观点。本文介绍并总结了儿童烟雾病流行病学、病因学、临床表现和治疗方案等相关的文献。

关键词 烟雾病;小儿神经外科;血管重建手术

中图分类号 R741;R651 **文献标识码** A **DOI** 10.16780/j.cnki.sjssgncj.20220285

本文引用格式:张新程,刘源,黄逸民,刘彦超,何学君,马小鹏,张华楸. 儿童烟雾病的临床概述[J]. 神经损伤与功能重建, 2023, 18(11): 656-661.

Clinical Overview of Pediatric Moyamoya Disease ZHANG Xincheng, LIU Yuan, HUANG Yimin, LIU Yanchao, HE Xuejun, MA Xiaopeng, ZHANG Huaqiu. Department of Neurosurgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

Abstract Moyamoya disease is a cerebrovascular disease characterized by chronic and progressive occlusion of the distal internal carotid artery. As the disease progresses, it often leads to ischemic or hemorrhagic stroke. The incidence of moyamoya disease is high in East Asia, with cases occurring in both children and adults. It is a relatively common cause of pediatric stroke. Moyamoya disease can be diagnosed through specific imaging findings on cerebral angiography. Effective pharmacological interventions to reverse or decelerate the progression of the disease are currently lacking. The primary treatment option for moyamoya disease is revascularization surgery, which significantly reduces the risk of stroke in patients. Previous studies mainly focused on the clinical aspects and treatments of moyamoya disease in adults. However, children with moyamoya disease exhibit differences from adults in clinical manifestations, surgical treatment strategies, and perioperative management. This review summarizes relevant literature on the epidemiology, etiology, clinical manifestations, and treatment approaches of pediatric moyamoya disease.

Keywords moyamoya disease; pediatric neurosurgery; revascularization

烟雾病(Moyamoya disease, MMD)是一种病因不明的慢性脑血管闭塞性疾病,由日本学者Takeuchi和Shimizu于1957年首次描述^[1],其特征是颈内动脉末端、大脑前动脉和大脑中动脉起始段双侧狭窄或闭塞,并伴有大脑底部异常侧支血管的形成^[2,3]。因其在脑血管造影上能观察到狭窄血管附近伴发异常侧枝血管,形似日语“一缕烟雾”而得名^[4]。60年来世界各地均有报道MMD病例,特别是在日本、韩国和中国等东亚国家最为高发^[5,6]。MMD是东亚地区最常见的儿童脑血管疾病,而儿童脑血管病又是导致儿童脑卒中的常见原因,其带来巨大的社会健康负担,并且是儿科神经系统疾病死亡的主要原因之一^[7,8]。但目前MMD的发病机制仍未完全了解,缺乏有效的预防手段,治疗方法也相对有限,儿童MMD更是存在着诊断、手术及围术期管理困难的问题^[9]。本综述主要关注儿童MMD的流行病学、临床表现、诊断和治疗方法的新研究,是国内首次系统地评价儿童MMD相关研究的临床综述,旨在提供

儿童MMD治疗与管理的新思路。

1 流行病学

近年来由于神经放射技术的发展及MMD的早期诊断识别,MMD在全球范围内患病率和发病率呈现逐年上升的趋势,这种趋势在东亚后裔中更明显,日本、中国和韩国是目前MMD患病率和发病率最高的国家^[5,6]。日本MMD年发病率由1994年的0.35/10万增加到2003年至2006年开展的研究所报道的0.94/10万,患病率由1994年的3.16/10万增加到2002年至2006年的10.5/10万^[10,11]。韩国MMD的年发病率从2007年的1.7/10万上升至2013年的4.3/10万,患病率从2007年的8.2/10万增加到2013年的18.1/10万^[12,13]。中国目前仍缺乏全国性的大样本量流行病学调查数据,局部地区的流行病学调查包括2000~2007年于南京市报道的患病率为3.92/10万的研究^[14]和2000~2011年于中国台湾地区开展的研究,这项研究报告了中国台湾地区2011年MMD的

患病率为1.61/10万,年发病率由2000~2001年的0.14/10万增加到2010~2011年的0.20/10万^[15]。这些流行病学研究指出人群中男性与女性的MMD患病率相似,且疾病分布具有一定的家族聚集性^[16]。日本所报道的家族性MMD的比例为10%~15%^[10,11,17,18],韩国最近的研究也报道了10%~15%的病例呈现家族聚集性^[19-21]。为了排除无症状MMD的干扰,2014年中国的一项研究对245例散发性MMD患者的直系亲属进行了经颅多普勒超声(TCD)筛查,确诊了41例家族性MMD,提示排除了无症状MMD后,家族性病例从7%增加到15%^[22]。地区分布则集中于东亚地区,在一项北美的研究中,MMD的发病率为0.086/10万,较亚洲地区更低,但美国亚裔的发病率却与亚洲地区的发病率相似^[23]。年龄分布表现为MMD相关的卒中事件有两个首次发病高峰,分别为儿童期和成人期^[24],并且儿童期的卒中事件发病高峰呈现出逐渐提前的趋势,日本地区的儿童期首次发病高峰年龄由1994年报道的10~14岁降低到2003~2006年所报道的5~9岁^[10,11],韩国地区的儿童期首次发病高峰年龄由2004~2008年报道的10~19岁降低到2007~2011年所报道的5~14岁^[12,25]。

2 病因学

目前,MMD的确切病因尚不明确,可能包括遗传因素、血管发育异常、免疫及炎症反应等。由于MMD存在一定的家族聚集性,故此认为遗传因素在病变发展的过程中可能起作用,研究较为广泛的主要是在血细胞和脾脏中表达的17q25.3上的无名指蛋白213(Ring Finger Protein 213, RNF213)^[26],包括RNF213 p.R4810K,RNF213 4810G>A和RNF213 4950G>A等的突变均与东亚人群MMD密切相关^[27,28]。最近的一项研究使用CRISPR-Cas9基因编辑技术生成了稳定的RNF213缺陷型人脑内皮细胞,发现RNF213敲除的人脑内皮细胞显示出明显的形态改变和血脑屏障通透性增加,同时伴有异常的诱导白细胞迁移潜力并分泌大量的促炎细胞因子^[29]。Ahel等^[30]发现MMD相关RNF213突变聚集在RNF213的复合E3结构域中,这可能干扰底物的泛素化。Sonobe等^[31]报道,敲除RNF213基因的小鼠不会自发地发展成MMD,这表明RNF213基因可能只是参与MMD的病理过程,而不是导致MMD的直接病因。Otten等^[32]的研究表明RNF213能够限制细胞溶质内沙门氏菌的增殖,在缺乏RNF213的细胞中,细菌不会吸引泛素依赖性自噬受体或诱导抗菌自噬,这可能解释了日本学者Suzuki等^[33]于1983年观察到的现象:100例MMD患者中有82.6%的儿童和61.1%的成年人患有头部或面部感染,这提示MMD的发生可能与机体对抗细菌的固有免疫有关。Suzuki等^[33]曾发现在MMD患者病变的血管壁中有IgG、IgM和C3等免疫介质的沉积,多项研究也发现MMD患者更易同时伴发自身免疫性疾病,如Grave病、系统性红斑狼疮等^[33-36],这提示MMD的发生可能与自身免疫因素有关。综上,MMD的病因可能是复杂且不单一的。

3 临床表现

MMD的临床表现包括短暂性脑缺血发作(transient

ischemic attack,TIA)、缺血性卒中、出血性卒中、癫痫发作、头痛和认知障碍等^[37]。儿童患者相较于成年患者更常出现缺血性卒中(包括失语、构音障碍、偏瘫等)与智力发育迟缓,出血性卒中较为罕见^[2,38]。Lee等^[39]分析了来自14个国家和32个地区的总共174例儿童MMD患者,其中90%的患儿出现缺血性卒中,7.5%的患儿出现TIA,2.5%的患儿出现出血性卒中。另一个值得关注的现象是儿童经常在过度换气,如哭闹及演奏乐器时,出现脑缺血症状(包括TIA及脑梗死),这是由于患儿在过度换气时会导致低碳酸血症,使包括病变血管在内的脑血管收缩,引发缺血性卒中^[40]。MMD对儿童认知能力和智力发育的影响往往被忽略,在一项研究中,Kuroda等^[41]测量了52例日本儿童患者的总智商(FSIQ评分),并与日本普通人群进行比较,发现MMD患儿的智力损害(定义为FSIQ评分<70)显著重于普通人群。通常只有出现卒中症状时患儿才会就诊,但智力损害往往发生地更早,所以及早发现并干预病程对患儿智力的发育至关重要^[42,43]。

4 诊断

MMD和烟雾综合征诊断与治疗中国专家共识编写组及国家卫生计生委卒中防治专家委员会缺血性卒中外科专业委员会于2017年已制定MMD和烟雾综合征诊断标准^[44]。

MMD诊断的金标准是数字减影血管造影(digital subtraction angiography,DSA)^[45]。MMD在脑血管造影上有其独特的影像学征象,表现为:双侧颈动脉系统存在颈内动脉末端和/或大脑前动脉、大脑中动脉起始部分狭窄或闭塞,并可在狭窄或闭塞病变附近发现异常血管网^[24,46]。对于无法配合行DSA者可使用磁共振血管造影(magnetic resonance angiography,MRA)进行替代^[45],这对儿童来说尤为重要。根据Suzuki制定的分期,可根据脑血管造影将MMD脑血管病变的严重程度分为6期^[46]。患儿两侧的Suzuki分期可以是不同的,且分期可在病程中不断变化。只累及一侧大脑半球血管的MMD称为单侧MMD,其中30%~40%将进展为双侧病变^[47,48]。

烟雾综合征是一类具有与MMD相似的脑血管造影表现,但与其他疾病相关或继发于其他疾病,如动脉粥样硬化、自身免疫性疾病、某些染色体疾病和结缔组织疾病等的疾病^[3]。国际儿科中风研究报告称,脑血管造影具有MMD特征儿童中有三分之一的患儿是继发于其他疾病的,最常见的相关疾病是镰状细胞性贫血、唐氏综合征和神经纤维瘤病1(neurofibromatosis type 1,NF1)^[3]。儿童患者中烟雾综合征的占比较成人高,烟雾综合征的治疗不同于MMD,其主要应针对原发病进行治疗,必要时也可手术干预。及时鉴别MMD与烟雾综合征有利于指导儿童治疗。

5 治疗

5.1 药物治疗

MMD目前尚无有效的药物可以进行防治^[44,45]。对于有卒中危险因素的进行性MMD,可预防性地使用抗凝药物及抗血

小板药物等。频繁癫痫发作的MMD患儿可使用抗癫痫药物控制症状发作^[8,49]。诊断为烟雾综合征的患儿,应针对相应原发病进行药物治疗,如对镰状细胞性贫血患儿使用羟基脲或输血治疗^[50-52]。

5.2 手术治疗

MMD的治疗主要是通过手术增加脑缺血部位的血流灌注,改善因缺血所致神经功能损伤^[53]。颅内外血管重建手术是MMD的主要外科治疗方法,分为三种类型:直接、间接和联合血运重建手术^[54]。近年来,已证实手术可有效降低缺血性及出血性卒中的风险,改善认知障碍^[55,56]。

5.2.1 术前评估 儿童因临床症状复杂及手术方案多变,需于术前进行广泛评估,包括临床评估及多影像组学评估^[57]。临床评估的目的是判断患儿是否存在其他基础性疾病及是否为烟雾综合征,烟雾综合征患者手术的并发症发生率较MMD患者更高^[58]。多影像组学评估包括使用脑血管造影术(DSA、MRA、CTA)了解疾病严重程度,侧枝血管的数量及位置^[45];使用灌注功能成像(单光子发射计算机断层扫描、PWI、CTP)评估低灌注区的范围及位置^[59],决定两半球手术的优先级;使用MRI、DWI等可以识别急性期脑梗死^[60],应推迟手术,以避免较高的并发症发生率;使用乙酰唑胺激发试验,可反映患儿脑血管储备情况^[61]。

5.2.2 手术时机 手术应在确诊后尽快进行,但应避免患儿卒中的急性期,一般在1~3月内完成手术即可^[62,63]。一项包含71例18岁以下患者的研究表明,诊断时年龄小(<4岁)和更高的MRA评分(>5分)代表着疾病进展迅速并易导致脑梗死,需要尽量于2月内完成手术^[64]。在韩国的一项研究中,与保守治疗相比,MMD患儿在症状发作后3月内进行手术干预以及在更年轻(<6岁)时进行手术已被证明可改善日常生活水平^[65]。

5.2.3 直接血管重建术 直接血管重建手术是通过引入颈外动脉系统的动脉血管作为供体,直接与颅内动脉系统吻合,使颈外动脉的血流可以直接补偿脑缺血区^[54]。根据患者缺血部位的不同,可选择颞浅动脉-大脑中动脉分支吻合术、大脑前动脉或大脑后动脉分支吻合术,当颞浅动脉不适合作为供体血管时,还可选用枕动脉或耳后动脉-大脑中动脉或大脑后动脉分支吻合术^[66]。供体血管最常使用颞浅动脉的额支或顶支,受体血管最常使用大脑中动脉M4段,可选取其中一只,也可使用两只做双侧吻合^[45,67]。直接血管重建术的优点是可以迅速建立起可靠稳定的侧枝血管,其缺点有:①需要较高的显微吻合技术,儿童的血管较成人更细更脆,管壁更加菲薄,增加了吻合难度。②通常当颞浅动脉的直径>1 mm时,认为可以进行血管吻合手术并保持长期通畅率^[68],在一项研究中,发现儿童患者的STA和MCA的最小直径可达0.7~0.8 mm^[69],这意味并非所有儿童都可进行直接搭桥手术。③直接搭桥术主要改善大脑中动脉供血区,术前经过影像学评估为大脑前、后动脉供血区缺血的患儿不能很好地从直接搭桥术中获益^[69,70]。④由于直接术式瞬时地增加了受体脑区的血流量,脑血管储备能力弱的儿童短时间内无法适应血流的激增,会出现高灌注综合征或再灌注损伤的风险^[71]。

5.2.4 间接血管重建术 间接血管重建手术的总体思路是将富

含血流的组织作为供体移植融合至脑缺血区域,通过缺血脑区释放的缺血信号和诱导血管生成的因子,以期待供体组织能够诱导新生血管形成并改善脑缺血,供体可选用血管组织带、去神经肌肉或硬脑膜等^[54]。术式包括:脑-肌肉血管融合术、脑-肌肉-动脉血管融合术、脑-硬脑膜-动脉血管融合术、脑-硬脑膜-肌肉-血管融合术、脑-硬脑膜-动脉-肌肉血管融合术、多点钻孔术等^[66,72]。直接血管重建术的优点有:①技术难度较低,不涉及显微血管吻合操作。②手术及麻醉时间短,患儿术后恢复快。③术中不临时阻断大脑中动脉皮质支,不会导致术中因操作所致的脑梗死。④可改善的缺血区域范围大且不局限于大脑中动脉供血区,额叶及枕叶缺血为主或广泛半球缺血时可首选间接搭桥术^[73]。⑤间接手术可以重复进行,当初次手术疗效不好时,可再次进行手术^[74]。⑥尽管术后短期内间接手术的改善差于直接手术,但随着时间的推移,间接手术能够建立强大的侧支循环,通常超过直接手术所能达到的程度^[75]。其缺点主要是形成新的侧枝代偿血管需要一定的时间,在这段时间内患儿仍暴露较大的脑梗死风险中,尤其是<4岁及MRA评分>5分者^[64,76]。值得一提的是多点钻孔术,它是对技术要求最低的血管重建术之一,通常在儿童患者中作为其他手术疗效不佳时的补救手术,可在局部麻醉下进行,对高手术及麻醉风险的患儿尤其适用^[77,78]。从长远效果来看,间接血管重建术对儿童MMD患者的意义更大^[53,75]。

5.2.5 联合血管重建术 联合血管重建术是指在一次手术中同时结合2种或以上的血管重建术式进行的手术,可以是直接手术联合间接手术,也可以是两种不同的间接手术联合使用^[66]。联合手术的优点有:①血管重建增加灌注量的程度大于单一手术,直接联合间接手术可以获得比单一手术更强大的血运重建。②血管重建增加灌注量的范围大于单一手术,联合间接手术可以弥补直接手术不能顾及大脑前、后动脉供血区的缺点。③可以同时获得短期及长期的血流灌注量增加。而缺点则是手术难度增加,手术时间延长及暴露于高灌注综合征的风险增加^[79]。

手术技术的选择取决于患儿的基础情况,缺血区域、范围,供受体血管的直径、血流量以及外科医生的技术专长和手术理念等。目前多数中心选择直接或联合血管重建手术^[69,80]。一项涉及1 448例儿童的系统综述发现直接或联合搭桥手术能获得比间接手术更好的影像学血管重建,但在改善临床症状上无差异^[81]。最近,一项涉及33项研究,4 197例病例的更长期临床结果的综述发现在随访5年和10年的儿科人群中,间接和联合手术之间的质量调整生命年没有显著差异,但两者都优于直接血管重建术^[82]。表明间接和联合手术可能在长期随访中提供更强的保护效应。

6 围术期管理

高碳酸血症和低碳酸血症都与MMD儿童神经系统并发症有关^[83,84]。低碳酸血症会降低整体的脑灌注压,而高碳酸血症会将血流优先分配至正常扩张的脑血管系统,导致不能正常扩张的狭窄脑血管产生盗血现象。整个围术期都应特别注意防

止儿童哭闹及过度换气,可以口服或静脉注射咪唑仑减轻患儿焦虑状态^[85]。术中严格控制呼气末CO₂分压(end-tidal CO₂, ETCO₂),有研究表示血管重建手术期间将ETCO₂控制在31~35 mmHg可缩短住院时间^[84]。此外,还要注意脑血管扩张剂的使用,这些药物也可产生盗血现象。

血压的管理对MMD并发脑卒中至关重要^[83,86],儿童大脑对氧气的代谢需求高于成人,除了要注意将MMD患儿整个病程中的血压维持在正常水平外,由于MMD患儿失去了正常儿童远低于成人安全血压水平以下便可获得足够脑灌注的特点^[87],加之MMD儿童对高血压的耐受性强于低血压,因此,建议将接受血管重建手术的MMD儿童术中平均动脉血压(mean arterial pressure, MAP)维持在基线的85%以内^[83]。直接手术中,夹闭大脑中动脉皮质支时,将MAP控制在高于基线5~10 mmHg的水平,保证临近部位充足的侧枝血管灌注,避免夹闭大脑中动脉皮质支可能造成的脑梗死^[87,88]。

体温升高会导致脑耗氧量的增加,发生求大于供的脑梗死,儿童的体温调节中枢尚未成熟,术后易出现吸收热,应给予关注^[89]。术中亚低温治疗降低脑耗氧量尚无明确证据证明可以降低MMD术中脑梗死的发生^[87]。

术后疼痛也可引起儿童脑耗氧量增加及过度换气^[90],因此,术中和术后的疼痛管理必须完善。

7 长期预后

血管重建手术对MMD患儿的保护效应是明确的,其能减少术后远期缺血性及出血性卒中的发生率,但仍存在一定的卒中发生风险^[56]。在一项平均随访了18.1年的长期研究中,作者报告了直接或联合血管重建术后的儿童患者中每年0.41%的晚期脑卒中事件发生率,10年、20年和30年的累积发病率分别为1.8%、7.3%和13.1%^[91]。另一项包含172例间接血管重建术治疗的儿童研究中,作者平均随访了14.3年,报告了6例患者(3.4%)在术后8年或更长时间发生了脑卒中事件。手术干预后10、20和30年迟发性卒中的累积风险分别为0.8%、6.3%和10.0%^[92]。虽然大多数患儿在手术后能够长期独立进行日常活动,但智力的损伤往往不被重视。一项包括56例儿童患者的研究中,接受手术治疗后仍有约10%的患者因智力障碍而在社交或学校生活中遇到严重困难^[93]。在另一项包含61例接受过联合搭桥手术MMD儿童的前瞻性研究中,作者平均随访了15.8年,报告了10例(17.9%)患儿仍继续存在社会适应困难,例如难以正常上学或就业^[94]。

8 结论

近年来随着影像技术的发展及医疗的普及,全世界范围内尤其是东亚地区所报道的MMD发病率呈现逐年增高的趋势。MMD存在两个年龄段的发病高峰,分别是成人期(30~40岁)及儿童期(5~15岁)。儿童MMD存在起病隐匿、诊断困难、发病症状重的特点,其常见的临床症状包括:缺血性脑卒中、TIA及智力发育障碍等,是导致儿科患者发生缺血性脑卒中最常见

的病因之一。儿童MMD的诊断除需临床表现符合外,还需要影像学的证据作为支持。DSA是诊断MMD的金标准,但为有创操作,不能配合完成DSA的儿童,可行MRA检查作为替代。MMD的病因目前尚不明确,且缺乏有效的药物治疗,颅内血管重建手术对儿童MMD患者再发脑卒中及智力发育的保护效应是明确的。颅内血管重建手术包括直接、间接和联合血管重建术,术式的选择应该根据不同患儿的基础情况、缺血区域及范围、供受体血管的直径、血流量以及外科医生的技术专长和手术理念等因素综合考量,越来越多的研究证明间接血管重建术对儿童MMD患者意义重大。

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(本文编辑:王晶)