

# 儿童偏头痛发病机制及治疗的研究进展

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## 摘 要

儿童偏头痛是儿童期常见的原发性头痛, 可严重影响患儿学习与身心发展。其发病与遗传易感性、皮层扩散性抑制、三叉神经血管激活、中枢致敏及肠-脑轴紊乱等多因素相互作用有关。本文在梳理相关机制研究进展的基础上, 系统综述生活方式管理、心理干预、NSAIDs及曲普坦等急性期用药, 以及托吡酯、赛庚啶、氟桂利嗪和CGRP单抗等预防及新型靶向治疗, 为儿童偏头痛的个体化规范管理与后续研究提供参考。

## 关键词

儿童偏头痛, 发病机制, 治疗进展

# Recent Advances in the Pathogenesis and Treatment of Pediatric Migraine

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## Abstract

Pediatric migraine is a common primary headache disorder in childhood and can markedly impair patients' academic performance and psychosocial development. Its pathogenesis involves the interaction of multiple factors, including genetic susceptibility, cortical spreading depression, activation of the trigeminovascular system, central sensitization, and dysregulation of the gut-brain axis. Building on recent advances in these mechanistic studies, this review systematically summarizes current evidence on lifestyle management and psychological interventions, as well as pharmacological strategies for both acute and preventive treatment. Non-steroidal anti-inflammatory drugs and triptans remain the main options for acute attacks, whereas topiramate, cyproheptadine, flunarizine and other agents, together with calcitonin gene-related peptide monoclonal antibodies, are used for prevention and represent emerging targeted therapies. These advances provide important implications for standardized, individualized management of pediatric migraine and inform future research directions.

## Keywords

Pediatric Migraine, Pathogenesis, Treatment Progress

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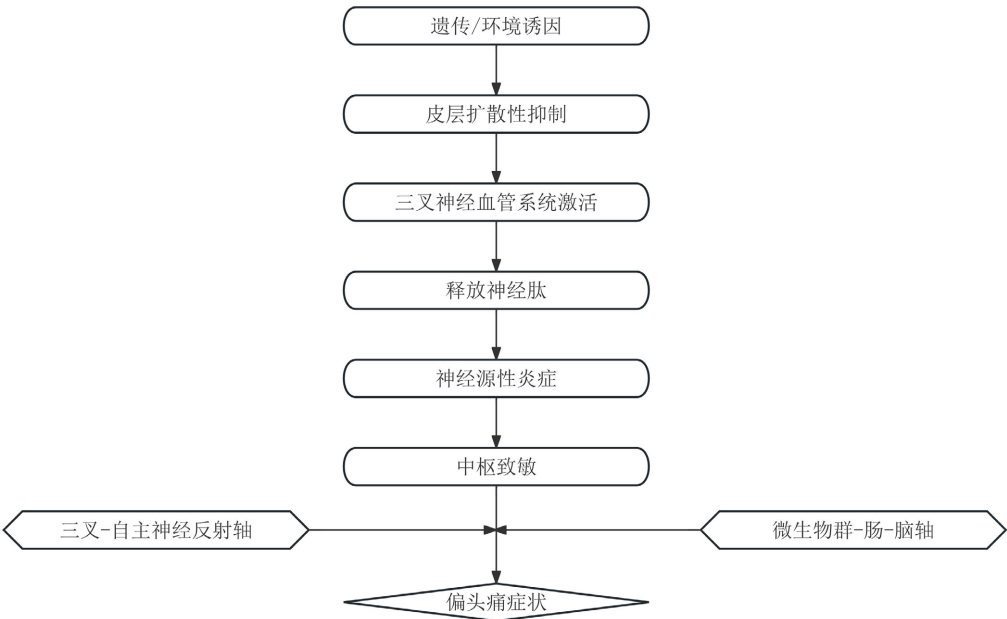
## 1. 引言

偏头痛(migraine)是儿科最常见的原发性头痛之一[1], 全球患病率约为 7%~11%, 并随年龄增长呈逐渐上升趋势[2] [3]。《国际头痛分类》第三版(International Classification of Headache Disorders, 3rd edition, ICHD-3), 将偏头痛分为无先兆偏头痛和有先兆偏头痛两大亚型。其中, 无先兆偏头痛典型表现为反复发作的头痛, 成人多持续 4~72 小时, 常为单侧、搏动性, 并伴有恶心、呕吐及畏光、畏声等症状; 有先兆偏头痛(经典型偏头痛)则在头痛前或同时出现可逆性的视觉、感觉或其他神经功能先兆, 先兆多持续约 15~20 分钟, 且视觉先兆占 90%以上[4] [5]。与成人相比, 儿童期偏头痛不仅起病年龄更早、病程波动性更大, 其发作常伴有恶心、呕吐、畏光、畏声等多样化表现, 而单次发作持续时间往往更短, 这些特征都增加了儿科临床对偏头痛的识别与分型难度[6]。反复发作的头痛可明显干扰患儿的学习和家庭生活, 还可能因反复疼痛体验、就诊频繁和家长焦虑而诱发或加重情绪与行为问题, 进而对神经心理发育和社会功能产生长期不利影响[1]。

目前, 偏头痛的发病机制尚不完全明确, 涉及遗传易感性、三叉血管系统激活、中枢及外周致敏、炎症及血管活性物质调控异常等多条途径的交互作用。鉴于偏头痛预后欠佳及发病机制不明确, 已成为研究热点和难点, 为此, 本文综述儿童偏头痛的发病机制和治疗进展, 为临床医生治疗偏头痛患者提供参考和借鉴, 并为后续个体化管理及机制性研究提供参考。

## 2. 儿童偏头痛的发病机制

儿童偏头痛的发生涉及遗传与神经兴奋性、皮层扩散性抑制、三叉神经血管系统与神经源性炎症、三叉 - 自主神经反射、中枢致敏以及微生物群 - 肠 - 脑轴等多系统的联合作用(如图 1)。



**Figure 1.** Schematic of integrated pathophysiology in pediatric migraine  
**图 1.** 儿童偏头痛综合病理生理机制示意图

**2.1. 遗传与神经兴奋性**

儿童偏头痛通常具有明确的遗传易感性，其发作可在多种诱因作用下被触发，如环境变化、睡眠节律紊乱或内分泌相关的生理因素等[7]。既往研究表明，若编码离子通道关键组分的基因发生突变，如CACNA1A、ATP1A2、SCN1A等，可导致离子通道功能受损及突触传递失衡，从而降低大脑皮层的兴奋阈值，为三叉神经-血管系统的激活提供有利条件，最终诱发偏头痛发作[8]。此外，近期研究还提示，血清素转运体(serotonin transporter)基因的变异可能与儿童偏头痛的性别差异相关，提示遗传因素在不同性别患儿中的作用机制可能并不完全一致[7]。总体来看，这些遗传与环境因素通过调节皮层兴奋性和神经网络可塑性，为后续皮层扩散性抑制(cortical spreading depression, CSD)及三叉神经-血管系统的激活奠定了一定的生物学基础。

**2.2. 皮层扩散性抑制**

CSD被公认为儿童偏头痛先兆的主要生理基础。其特征是在大脑皮层发生一股缓慢传播的“去极化—抑制”波：局灶区域内神经元与胶质细胞几乎同步强烈去极化，随后该去极化波呈同心性沿皮层扩延，所经区域出现持续数分钟的神经元活动抑制，并伴随相应的脑血流改变[9]。若传播至枕叶视觉皮层，即可产生典型的视觉先兆；进一步向邻近顶叶、颞叶等区域扩延时，则出现与受累皮层功能相一致的其他先兆表现。除引发先兆外，CSD还可能通过两条途径参与头痛发生：其一，直接激活三叉神经颈复合体(trigemino-cervical complex, TCC)，增强三叉神经-血管系统的兴奋性；其二，通过局部释放致痛与促炎介质并改变离子微环境，提高脑膜感觉纤维的反应性，从而触发偏头痛样头痛[10]。因此，CSD不仅是皮层功能异常的局部表现，更是连接“遗传因素”与“三叉神经血管系统”的关键枢纽事件。

**2.3. 三叉神经血管系统与神经源性炎症**

三叉神经血管系统的活化及其引发的神经源性炎症被认为是儿童偏头痛发生的重要病理生理基础。当分布于脑膜及脑膜血管的三叉感觉神经末梢受到刺激后，可释放降钙素基因相关肽(calcitonin gene-

related peptide, CGRP)、P 物质等多种神经肽, 继而引起脑膜血管扩张、血管周围感觉神经敏感性增高, 并将痛觉信号传入中枢, 从而产生偏头痛样头痛[11]。部分研究观察到, 儿童偏头痛患儿在发作期外周或血浆 CGRP 水平明显升高[12], 这提示其神经源性炎症反应可能较成人更为突出, 也从机制层面为 CGRP 通路相关的靶向治疗在儿童偏头痛中的应用提供了支持[13]。由此可见, 三叉神经血管系统的激活与神经源性炎症不仅将源自 CSD 和多种外周诱因的信号转化为强烈而持续的痛觉输入, 也为后续中枢致敏及三叉-自主神经反射的募集提供了持续驱动力。

## 2.4. 三叉-自主神经反射

儿童偏头痛通常并非仅以疼痛为唯一表现, 部分患儿可合并颅面部自主神经症状(cranial autonomic symptoms, CAS), 如流泪、结膜充血、鼻塞/流涕与瞳孔缩小等[14]; 尽管 CAS 传统上被视为三叉-自主神经性头痛(trigeminal autonomic cephalalgias, TACs)的特征, 近年研究表明在儿童偏头痛人群中亦相当常见[15], 且其存在可能影响治疗反应与预后[16]。三叉-自主神经反射弧是 CAS 的关键枢纽: 偏头痛发作时, 三叉神经初级传入纤维激活 TCC, 继而驱动脑干上泌涎核(superior salivatory nucleus, SSN), 经面神经副交感通路募集翼腭(蝶腭)神经节(sphenopalatine ganglion, SPG); SPG 对泪腺、鼻腔/腭黏膜及颅内血管发出副交感纤维, 释放乙酰胆碱、血管活性肠肽(vasoactive intestinal peptide, VIP)和一氧化氮(NO), 导致血管扩张与腺体分泌增强, 从而产生上述 CAS [17]。

## 2.5. 中枢致敏

既往研究表明, 神经源性炎性刺激诱发三叉神经外周系统的外周致敏: 三叉神经节的神经-胶质单元内 MAPK、NF- $\kappa$ B 等信号通路被激活 CGRP 等神经肽及促炎细胞因子上调, A $\delta$ /C 纤维兴奋性升高, 从而在硬脑膜相关结构形成机械与温度敏化, 并经初级传入上行驱动三叉神经脊髓束核尾侧部(trigeminal nucleus caudalis, TNC) [18]。持续的外周输入进一步使 TNC 神经元放电阈值下降、反应性增强, 表现为中枢致敏, 致使原本无害的轻触刺激(如梳头、戴眼镜)即可诱发触痛或是引出偏头痛发作[19]。在儿童人群中, 此类敏化现象往往更为常见且发作更频繁、程度更重[17], 不仅降低急性与预防性药物治疗的疗效, 还可能促进偏头痛的慢性化与病程进展[20]。

## 2.6. 微生物群-肠-脑轴

肠道微生物群(gut microbiota)是随时间动态变化的共生菌群, 对儿童的生长发育与免疫成熟至关重要[21]; 越来越多证据表明, 其通过“肠-脑轴”以直接和间接方式参与儿童偏头痛的发生与维持[22]。直接证据来自动物模型: 肠道微生物组成的改变、短链脂肪酸(short-chain fatty acids, SCFAs)谱的波动以及促炎/抗炎细胞因子释放的不平衡, 均与偏头痛样疼痛行为相关。间接证据则包括益生菌与特定饮食干预在部分研究中的有益信号, 以及经迷走神经调节所显示的症状改善, 提示基于微生物组的干预可能成为偏头痛管理的辅助手段[23]。近期研究进一步指出, 儿童偏头痛与肠道菌群失调相关, 这一关联有助于解释偏头痛与功能性胃肠道疾病在儿童中的常见共存现象[24], 并为阐明其病理生理机制与探索个体化治疗策略提供了新的思路。

# 3. 儿童偏头痛的治疗

## 3.1. 非药物治疗

### 3.1.1. 生活方式干预

在儿童偏头痛的非药物治疗中, 生活方式干预是核心策略: 第一, 压力被证实与头痛发作明确相关[25], 急性压力可触发至少一半的发作事件, 且学业压力、惩罚式教育、家庭冲突及家长抑郁等因素显著

增加患儿风险[26]; 第二, 不规律饮食与更频繁且更严重的头痛相关, 而体重管理与均衡膳食有助于降低发作风险[27], 最新研究发现, 生酮饮食在部分研究中显示潜在获益, 但应在专科团队监测下个体化、限期尝试[28]; 第三, 良好的睡眠有助于避免偏头痛的慢性化, 有研究发现可以通过固定就寝一起床节律、营造舒适的睡眠环境来降低头痛风险, 而失眠或睡眠时长小于 8 小时与头痛风险升高相关[29]; 第四, 有氧运动是头痛管理的重要因素[25], 研究发现偏头痛儿童往往运动量较少, 至少 50% 的患者肥胖或超重[30], 而研究表明, 体育锻炼和体重管理有助于减少偏头痛的发作频率与强度[31]; 最后, 多项研究将电子屏幕暴露视为潜在风险因素[32], 建议限制娱乐性屏幕时长、设置“无设备时段”并强化家长监督, 以减轻诱发风险[33]。总体而言, 将压力管理、规律饮食、睡眠卫生、规律有氧运动与体重管理, 以及规范屏幕暴露整合为连续、可操作的生活方式干预方法, 并贯穿健康教育与自我监测, 可在不增加药物负担的前提下降低发作频率与严重程度, 为药物治疗与长期预防提供坚实基础。

### 3.1.2. 认知行为疗法

认知行为疗法(cognitive behavioral therapy, CBT)是儿童偏头痛管理中证据充分的一线非药物干预之一, 其通过整合认知重构、行为技能训练、诱因管理与情绪调节等技术, 旨在同时改善与头痛相关的环境触发因素、负性认知与应激反应[34]。多项研究显示, CBT 可显著降低头痛发作频率与强度、减少功能受限, 并提高自我管理能力和[35]; 与此同时, 部分临床试验提示, CBT 与预防性药物(如阿米替林)联合较单纯药物治疗可进一步减少头痛天数、提升应对效能[36]。基于其安全性与可操作性, 临床实践中宜将 CBT 与健康教育及生活方式干预一并纳入标准化路径, 必要时与个体化的药物预防方案配合, 以降低发作负担的同时改善长期功能结局。

### 3.1.3. 神经调控

神经调控(neuromodulation)是近年来偏头痛领域发展较快的一类非药物治疗手段, 主要通过电刺激、磁刺激或化学刺激等方式调节中枢及外周神经环路的兴奋性, 从而影响疼痛的发生与传导[37]。常用技术包括经皮眶上神经刺激(transcutaneous supraorbital neurostimulator, tSNS)、单脉冲经颅磁刺激(single-pulse transcranial magnetic stimulation, sTMS)等[38]。研究表明, sTMS 通过向枕叶或相关皮层发放单次磁脉冲, 有望干预皮层扩散性抑制并降低偏头痛发作的频率和严重程度, 在儿童和青少年中总体耐受性良好, 尚未发现严重安全事件, 但现有疗效数据仍然有限[39]。除 sTMS 外, 非侵袭性迷走神经刺激(non-invasive vagus nerve stimulation, nVNS)通过电刺激颈部或耳廓迷走神经分支, 可为不能耐受或不愿长期口服药物的患儿提供潜在选择; 外周三叉神经电刺激(electrical trigeminal nerve stimulation, eTNS)则直接作用于三叉神经, 部分研究显示其可降低偏头痛发作频率且在儿童中耐受性较好。近年来兴起的远程电神经调控(remote electrical neuromodulation, REN), 在急性发作时使用不仅能够缓解当次发作症状, 其规律应用还与每月治疗日数减少相关, 提示可能具有一定的预防获益[40]。

## 3.2. 药物治疗

### 3.2.1. 急性期治疗

非甾体抗炎药(NSAIDs)仍为儿童偏头痛急性期的一线用药[41]。对乙酰氨基酚与布洛芬在小于 12 岁人群的急性管理中总体安全且具有一定有效性[42]; 荟萃分析显示, 布洛芬在发作后 2 小时内缓解疼痛的有效性优于安慰剂, 而对乙酰氨基酚在 2 小时结局上的获益证据相对不一致[43]。阿司匹林虽可缓解偏头痛, 但因与急性非炎性脑病相关的潜在风险, 不推荐用于儿童与青少年[44]。对于 NSAIDs 应答不足者, 可考虑单用或联合使用曲普坦类药物[41]。曲普坦作为选择性 5-HT<sub>1B/1D</sub> 受体激动剂, 通过抑制三叉通路上行痛觉传递并减少外周促炎递质释放而发挥作用。美国食品药品监督管理局(FDA)将利扎曲坦

(Rizatriptan)作为 6~17 岁偏头痛人群的用药, 阿莫曲坦(Almotriptan)与佐米曲坦(Zolmitriptan)则需在 12 岁以上的人群使用, 而目前尚无针对 6 岁以下儿童的曲坦类药物获批[45]。麦角类药物在部分难治性发作或偏头痛持续状态中可作为选项, 但受限于不良反应及禁忌证, 需谨慎个体化使用[46]。

### 3.2.2. 预防性治疗

现有研究指出, 托吡酯可以用于 12~18 岁青少年的预防治疗[47], 但进一步研究发现其在减少头痛日方面与安慰剂差异不显著, 需谨慎权衡体重下降、乏力与认知影响等不良反应[48]; 部分抗癫痫药物在儿童预防中显示潜在效益, 如丙戊酸钠在有限资料中可呈现与成人相近的预防效果, 但其致畸与卵巢不良反应限制育龄女童使用[49]; 左乙拉西坦的初步研究提示可降低发作频率和致残度, 惟依从性与易激惹问题仍需更大样本随机对照试验验证[50]。经典预防药物中, 赛庚啉与氟桂利嗪在儿童人群整体耐受性与疗效信号较为可接受, 但需关注嗜睡、体重增加等不良反应[51]; 普萘洛尔虽缺乏高质量儿科证据却在临床应用广泛, 但使用过程中应监测心动过缓与低血压, 且哮喘患儿应避免[52]。针对 CGRP 通路的单克隆抗体近年来作为预防性治疗显示前景[53], 但儿科安全性与有效性仍需进一步验证与长期随访[53]。综上, 预防管理应以“足量足疗程评估-个体化选择-重视不良反应与 CBT 及生活方式干预并行”为基本策略, 在确保安全的前提下最大限度降低头痛负担与功能损害。

## 4. 总结

总之, 儿童偏头痛是一种以遗传易感性为基础、受多重环境与生理诱因共同调控的疾病, 循证实践支持在生活方式管与认知行为疗法等心理干预的基础上, 联合个体化的急性期与预防性药物方案, 以协同降低发作频率与强度、减少功能受限并控制急性用药负担, 从而降低慢性化风险。未来研究亟需高质量、多中心的前瞻性队列与随机对照试验, 从遗传学、神经影像与神经炎症等维度进一步阐明特异机制, 建立可推广的生物标志物与风险分层体系, 并据此优化不同年龄段与表型患儿的精细化管理路径, 同时强化长期安全性与结局的系统评估。

未来研究亟需在机制和临床之间实现更紧密的衔接: 一方面, 通过长期随访和真实世界研究, 系统评估儿童期应用 CGRP 靶向药物对神经系统发育及全身生长的远期安全性, 明确不同年龄和表型患儿的获益与风险; 另一方面, 基于可穿戴设备和多模态生理信号, 构建并验证适用于家庭与学校场景的早期预警和发作预测模型, 引入人工智能技术提升个体化管理水平。同时, 应进一步识别遗传易感性、CSD、三叉神经血管激活、中枢致敏以及微生物群-肠-脑轴紊乱之间的关键网络枢纽, 结合多组学、生物标志物和神经影像学手段推动机制分型和风险分层, 并在此基础上系统评价饮食干预等微生态调节策略与生活方式管理、药物治疗及神经调控技术的协同效应, 从而构建安全可行、长期可持续的综合管理路径, 以期实现对儿童偏头痛病程及长期神经心理结局的整体优化。

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