

血液透析患者皮肤瘙痒发病机制的研究进展

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摘要

慢性肾脏病相关性瘙痒(CKD-associated Pruritus, CKD-aP), 又称尿毒症性瘙痒症(Uremic Pruritus, UP), 是维持性血液透析患者常见的并发症, 严重影响患者的生活质量, 并与不良预后相关。其在血液透析患者中的患病率高达22%~84%。尽管近20年来透析技术不断进步, 但中重度瘙痒的患病率仍维持在20%~40%。目前研究表明, CKD-aP的发病机制涉及多因素交互作用: 皮肤干燥症通过破坏皮肤屏障、降低瘙痒阈值加剧症状; 免疫炎症失调表现为辅助性T细胞1 (T helper 1 cell, Th1)、白细胞介素-6 (Interleukin-6, IL-6)、白细胞介素-31 (Interleukin-31, IL-31)等炎症因子升高, 驱动系统性炎症反应; μ -阿片受体(μ -Opioid Receptor, MOR)过度激活与 κ -阿片受体(κ -Opioid Receptor, KOR)表达减少, 打破瘙痒调节平衡; 尿毒症毒素(如硫酸吡哆酚、甲状旁腺激素、磷酸钙等)累积直接或间接激活神经纤维与炎症通路; 神经系统紊乱涉及瞬时受体电位香草酸亚型1 (Transient Receptor Potential Vanilloid 1, TRPV1)、T型钙通道亚型Cav3.2 (Cav3.2)等离子通道异常及神经营养因子失衡, 导致瘙痒信号传导异常。此外, 环境污染物及个体差异等亦参与发病。尽管现有证据揭示了多维度机制, 但各因素间的协同作用仍需深入探索, 这为开发针对性的治疗策略提供了潜在方向。

关键词

慢性肾脏病相关性瘙痒, 血液透析, 尿毒症性瘙痒症, 发病机制

Research Progress on Pathogenesis of Skin Pruritus in Patients with Hemodialysis

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Abstract

Chronic Kidney Disease-associated pruritus (CKD-aP), also known as Uremic Pruritus (UP), is a common complication in patients undergoing maintenance hemodialysis, significantly impairing quality of life and associated with poor prognosis. Its prevalence among hemodialysis patients ranges from 22% to 84%. Despite advances in dialysis technology over the past two decades, the prevalence of moderate to severe pruritus remains between 20% and 40%. Current evidence indicates that the pathogenesis of CKD-aP involves multiple interacting factors: xerosis cutis exacerbates symptoms by disrupting the skin barrier and lowering the itch threshold; immune-inflammatory dysregulation manifests as elevated inflammatory factors such as T helper 1 (Th1) cells, Interleukin-6 (IL-6), and Interleukin-31 (IL-31), driving systemic inflammatory responses; imbalance in the opioid system, characterized by overactivation of μ -Opioid Receptors (MOR) and reduced expression of κ -Opioid Receptors (KOR), disrupts the equilibrium of itch modulation; accumulation of uremic toxins (e.g., indoxyl sulfate, parathyroid hormone, calcium-phosphate complexes) directly or indirectly activates nerve fibers and inflammatory pathways; nervous system dysregulation involves abnormalities in ion channels such as transient receptor potential vanilloid 1 (TRPV1) and Cav3.2, along with imbalances in neurotrophic factors, leading to aberrant itch signaling. Furthermore, environmental pollutants and individual differences also contribute to disease manifestation. Although existing evidence highlights multidimensional mechanisms, the synergistic interactions among these factors warrant further investigation, offering potential directions for developing targeted therapeutic strategies.

Keywords

Chronic Kidney Disease-Associated Pruritus (CKD-aP), Hemodialysis, Uremic Pruritus (UP), Pathogenesis

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1. 引言

慢性肾脏病(Chronic Kidney Disease, CKD)相关性瘙痒(CKD-associated pruritus, CKD-aP), 既往又被称为尿毒症性瘙痒症(Uremic Pruritus, UP), 是接受血液透析治疗终末期肾病患者常见的并发症之一。CKD-aP 在血液透析人群中的患病率差异较大, 约为 22%~84%, 其中约 20%~40%的患者报告中度至重度瘙痒[1]。一项国际透析结局和实践模式研究(Dialysis Outcomes and Practice Patterns Study, DOPPS)数据显示, 尽管近二十年来透析技术不断进步, 中重度瘙痒的患病率已从早期的 45% (DOPPS 1 期, 1996~2001)下降至近年的 37% (DOPPS 4~6 期, 2009~2018), 但其临床负担依然沉重[1]-[3]。CKD-aP 不仅严重影响血液透析(HD)患者的身心健康及生活质量, 还引发情绪烦躁、睡眠障碍、抑郁, 严重者甚至导致自杀[4]-[7]。此外, 研究显示, 有瘙痒的血液透析患者全因死亡率、心血管事件发生率、感染相关死亡率及住院率均显著高于无瘙痒者[2] [8]。尽管危害显著, 但临床上仍存在诊断不足、治疗不规范的问题。据研究, 在持续存在中重度瘙痒的患者中, 18%的患者未接受瘙痒治疗, 17%的患者没有向医护人员报告瘙痒, 69%的医护人员对其所在病房的瘙痒患病率亦常低估[9]。目前 CKD-aP 在临床上仍常被忽视, 其确切的发病机制尚未完全阐明, 导致缺乏特效治疗方法。因此, 本文旨在系统综述 CKD-aP 发病机制的最新研究进展,

以期深入阐明其病理生理机制和开发靶向治疗策略提供理论依据。

2. CKD-aP 的临床表现及其诊断

CKD-aP 的临床表现具有多样性,呈发作性,夜间较白天加重,可持续数月或甚至数年,且通常呈对称性或全身性分布,也可局部分布,主要见于背部、面部和动静脉内瘘侧上肢等部位,皮肤以干燥和鳞屑为主要表现,脓疱、结痂、丘疹、溃疡和结节等表现较为少见[6] [10]-[13]。瘙痒不具有特定的皮肤节段分布,且可因干燥、温度变化(热和冷)、压力以及淋浴等多种因素加重瘙痒症状[14]。约 61% 的患者表示瘙痒与透析时间无关,但仍有约 24% 的患者表示在透析期间或透析后短期内症状明显[10] [14]。CKD-aP 的诊断需排除原发性皮肤病、慢性肝病、胆汁淤积、内分泌及代谢性疾病、血液系统疾病、感染、药物、实体肿瘤、躯体障碍等可能引发瘙痒的相关因素[15]。目前中国第一个《慢性肾脏病相关瘙痒管理中国专家共识(2025)》给出的诊断标准如下:① CKD 患者出现瘙痒,排除有明确证据证明瘙痒由其他疾病所致;② 2 周内至少有 3 d 出现瘙痒,且每天出现数次,每次持续数分钟,影响患者生活;③ 瘙痒症状反复出现,持续至少 6 周。诊断该病需同时满足以上 3 个条件[16]。

3. CKD-aP 的发病机制

3.1. 皮肤干燥症及其他皮肤病

皮肤干燥主要表现为鳞屑、粗糙、开裂和裂缝,在 CKD 患者中特指尿毒症干燥症,并非 CKD-aP 的首要病因。但在已存在瘙痒的前提下,皮肤干燥通过降低瘙痒的阈值而加剧瘙痒[17] [18]。研究显示,在慢性肾功能衰竭患者中,皮肤干燥症在瘙痒人群中的患病率(109/197)显著高于非瘙痒组(80/185),进一步支持两者的关联性[19]。在 CKD-aP 人群中,皮肤干燥症发生的主要原因可能与皮脂腺及外分泌汗腺萎缩、基底区增厚、角质层 pH 值失衡及脂质组成改变等相关,加之透析过程中液体移位,皮肤水合作用降低,这些因素导致皮肤屏障作用失调,对外界刺激及内源性致痒物质的敏感性升高[20]-[23]。此外,皮肤微血管病变也可能参与发病,该病变以小血管结构重塑及功能障碍为特征,受尿毒症毒素蓄积、慢性炎症等多种因素驱动,从而引发组织缺氧、氧化应激及血管生成紊乱,最终导致毛细血管稀薄和纤维化,进一步加重皮肤营养供应障碍及屏障损伤,间接参与瘙痒的加剧过程[24]。值得注意的是,CKD-aP 患者持续搔抓可引发皮肤损伤、继发感染及慢性炎症,这可能进一步加重原有病情,致使瘙痒与搔抓两者形成恶性循环,产生继发性皮肤病变[20]。需强调的是,搔抓是瘙痒导致的继发行为,其本身不会诱发慢性肾功能衰竭。关于皮肤微生物组学与 CKD-aP 的关联,高瘙痒组与低瘙痒组间背部皮肤微生物群的整体组成无显著差异,提示皮杆菌与 CKD-aP 的具体关联可能尚需更大样本、多中心研究验证[25]。脂质运载蛋白 2 (Lipocalin-2, LCN2) 在 CKD 患者表皮和真皮附件中的表达显著增加,与瘙痒严重程度、CKD 分级显著相关,并且随着瘙痒严重程度的改善,患者组织和血清 LCN2 水平显著降低,提示 LCN2 可能通过调控皮肤炎症反应及角质形成细胞分化参与 CKD-aP [26]。研究发现,蛋白酶激活受体-2 (Protease-Activated Receptor-2, PAR-2) 在终末期肾病患者表皮,尤其是上表皮的表达显著上调[27]。蛋白酶激活受体(Protease-Activated Receptors, PARs)是一类 G 蛋白偶联受体,其中 PAR-2 与急性炎症反应相关且不依赖于组胺引发瘙痒。多项研究表明,皮肤干燥可能通过降低皮肤瘙痒阈值加重 CKD-aP 症状,外用润肤剂可通过改善皮肤水合状态、修复屏障功能缓解部分患者的瘙痒,但并非所有皮肤干燥的 CKD 患者均伴有瘙痒,这意味着皮肤干燥可能只是瘙痒的加剧因素,而非直接病因[20] [24] [28]。

3.2. 免疫与炎症

越来越多的证据提示,CKD-aP 并非单纯的皮肤症状,而是以全身系统性慢性炎症为核心特征的疾病

[10][13][24][29]-[32]。免疫炎症因子表达上调和免疫细胞浸润异常在血液透析患者中尤为明显,提示免疫炎症失调是 CKD-aP 的关键潜在病因[13]。在血液透析合并瘙痒的患者中,辅助性 T 细胞 1 (T helper 1 cell, Th1)、C 反应蛋白(C-Reactive Protein, CRP)、白细胞介素-6 (Interleukin-6, IL-6)和白细胞介素-2 (Interleukin-2, IL-2)、干扰素- γ (Interferon- γ , IFN- γ)等炎症物质水平显著升高[24][33]-[35]。此外,CKD-aP 的发展和严重程度与高白细胞、高铁蛋白、低血清转铁蛋白及低白蛋白水平相关的炎症反应密切相关[33][35]。这些证据进一步提示了系统性炎症在 CKD-aP 发病中的作用。从局部皮肤炎症反应层面来看,CKD-aP 患者嗜酸性粒细胞、肥大细胞和已知的瘙痒原、组胺和胰蛋白酶水平升高[20][32][36][37]。值得强调的是,尽管有组胺参与,但 CKD-aP 患者缺乏荨麻疹等经典的组胺特异性皮肤变化,传统抗组胺药物治疗效果甚微,并且大多数旨在减少组胺释放的临床试验均呈阴性结果,提示组胺可能并非 CKD-aP 的主要介导因子[10][20][36][37]。近年来,特定细胞因子通路的作用备受关注。白细胞介素-31 (Interleukin-31, IL-31)作为一种新型细胞因子,已被证明参与皮肤炎症、气道超敏反应及多种瘙痒性疾病的发病机制,阻断 IL-31 或其受体的抗体可缓解瘙痒,其血清水平与 CKD-aP 患者瘙痒有关[38]-[42]。IL-31 受体拮抗剂奈莫珠单抗(Nemolizumab)在特应性皮炎中达到了III期临床试验,但在 CKD-aP 中的疗效仍需更多证据支持[42]-[44]。此外,IL-6/p-BTK/p-ERK 的信号转导介导磷酸钙引起 CKD 患者瘙痒,为后续治疗提供了新的靶点,揭示了矿物质代谢异常与免疫炎症交织的另一致病途径[45]。临床干预证据进一步支持炎症机制的核心地位。沙利度胺、他克莫司、环孢素等免疫抑制剂及窄谱中波紫外线对部分 CKD-aP 患者的瘙痒症状具有明确改善作用[30][46]-[48]。观察性研究表明,接受免疫抑制治疗的肾小球病变患者瘙痒发生率较低,以及饮食干预(如素食)可能通过减轻微炎症状态而改善瘙痒,均为炎症假说提供了间接佐证[24][49][50]。除内源性因素外,外部环境也可能加重炎症负荷。一项横断面研究表明,二氧化氮(Nitrogen Dioxide, NO₂)和一氧化碳(Carbon Monoxide, CO)等环境污染物可能与维持性血液透析(Maintenance Hemodialysis, MHD)患者 CKD-aP 风险增加有关,强调了环境因素在其瘙痒发病机制中的重要性[51]。其机制可能在于这些污染物可诱发或加剧氧化应激,并激活炎症小体,从而放大 CKD 患者既有的系统性低度炎症状态,间接参与 CKD-aP 的发生过程。总之,免疫炎症机制在 CKD-aP 中扮演着重要的角色,但其确切的作用机制仍有待进一步阐明和探索。

3.3. 阿片系统失调

近年来研究表明,内源性阿片系统不仅参与疼痛调节,在瘙痒的发生与调控中也发挥关键作用。阿片受体主要有三种亚型: μ -阿片受体(μ -Opioid Receptor, MOR)、 κ -阿片受体(κ -Opioid Receptor, KOR)和 δ -阿片受体(δ -Opioid Receptor, DOR)[24][52]。其中,MOR 的过度激活具有促痒效应,而 KOR 的激活则可抑制瘙痒,且 KOR 的激活可抑制中枢和外周的 MOR 活性[24][32][53][54]。一项纳入 40 例 HD 患者的研究显示,21 例瘙痒患者的皮肤组织中 KOR 表达水平显著低于 19 例无瘙痒患者,且瘙痒严重程度与表皮 KOR 定量表达呈负相关[55]。值得注意的是,内源性阿片系统与免疫炎症系统之间存在密切的双向调控关系。炎症状态的变化会影响外周阿片受体的表达,且炎症微环境可增强阿片类物质的镇痛效应[56]。反之,多种免疫细胞(包括粒细胞、单核细胞/巨噬细胞及淋巴细胞)表面均检测到阿片受体的表达[56]-[62]。免疫细胞(包括单核细胞和 T 淋巴细胞)阿片受体的激活,可减少前列腺素等促炎物质的释放,进而诱导抗炎反应,而前列腺素本身亦是重要的致痒介质[20][63][64]。此外,阿片受体激动剂或拮抗剂的药理作用可能因组织炎症状态的不同而存在差异,这一特性在 CKD-aP 的病理生理过程中可能同样存在[24][56]。因此,深入解析阿片系统与免疫炎症系统的交互调控机制,对阐明 CKD-aP 的复杂病理生理过程、开发靶向阿片受体平衡的治疗策略具有重要的理论与临床意义。

3.4. 尿毒症毒素和其他物质累积

CKD 患者的肾小球滤过率(Glomerular Filtration Rate, GFR)下降, 导致尿毒症毒素及代谢产物在体内蓄积被认为是 CKD-aP 发生的机制之一[20]。肾移植可显著增加尿毒症毒素清除, 进而改善多数患者的瘙痒症状, 间接印证了清除累积毒素对改善瘙痒的关键作用[65]。目前研究较多的潜在致痒相关物质包括甲状旁腺激素(Parathyroid Hormone, PTH)、钙、磷、铝、 β_2 微球蛋白等[1] [10] [36] [66]-[75]。尽管继发性甲状旁腺功能亢进(Secondary Hyperparathyroidism, SHPT)患者中 CKD-aP 患病率较高, 但并非所有 CKD-aP 患者均合并 SHPT, 且针对 SHPT 的治疗(包括甲状旁腺切除术)也并非总能缓解瘙痒症状, 外源性 PTH 注射亦未直接引发瘙痒[20] [30] [71] [76]。这表明 PTH 可能并非直接致痒分子, 其致痒作用更可能与它引起的钙磷代谢紊乱相关。血磷过高可与血清钙结合形成磷酸钙, 沉积于皮肤和其他组织, 进而激活局部神经纤维诱发瘙痒[20] [77]。研究显示, CKD-aP 患者表皮基底层细胞外游离钙离子浓度显著高于无瘙痒者, 而高血清铝离子水平也被发现是瘙痒的独立危险因素(比值比 = 5.64) [78] [79]。尽管提高透析效率是清除毒素的有效手段, 多数研究发现提高透析充分性指标 Kt/V (尿素清除指数)可降低 MHD 患者 CKD-aP 的患病率和程度, 但也有多项研究未复现该结论, 亦有瘙痒程度与 PTH、钙、磷等指标无显著相关性 [2] [80]-[84]。除传统的小分子及中分子毒素外, 晚期糖基化终产物(Advanced Glycation End products, AGEs)作为在高血糖和慢性肾脏病(CKD)中蓄积的异质化合物, 可通过与其受体(Receptor for AGEs, RAGE)结合, 激活下游 NF- κ B 等信号通路, 促进氧化应激与促炎细胞因子(如 IL-1 α 、IL-6)的释放[85]。研究表明, AGEs 在 CKD-aP 患者皮肤角质层异常堆积, 推测其可能是连接代谢紊乱、持续性微炎症与瘙痒的潜在途径之一[86]。

近年来, 代谢组学研究为理解毒素谱提供了新视角。研究发现, 瘙痒严重程度不同的患者之间存在特征性代谢物差异, 其中磷脂、尿毒症毒素和类固醇的组合对区分两者具有较高的准确性(Area Under the Curve, AUC = 0.899) [87]。另一项研究发现, 酯类、油酸酯类和甘油酯类代谢物在瘙痒患者中显著升高 [88]。然而, 亦有代谢组学研究并未发现特异性差异, 这提示该领域仍需大样本、多中心研究验证[89]。单一尿毒症毒素与 CKD-aP 的关联性存在争议且结论不一。这表明, 瘙痒可能并非由某一种特定毒素直接引起, 而是多种毒素共同作用、并与机体其他系统(如免疫、神经系统)相互作用的结果。提高透析充分性虽能改善部分患者症状, 但无法完全缓解, 也印证了其机制的复杂性。

3.5. 神经系统紊乱

神经系统功能紊乱被认为可能是 CKD-aP 的发病机制之一。普遍认为, 瘙痒的产生是源于皮肤感受器或外周神经末梢受到刺激后产生电信号, 该信号经 C 纤维传入到脊髓背角, 经过特定神经元整合处理后, 沿脊髓丘脑通路上行投射至大脑皮层及其他相关区域, 最终产生瘙痒感知[90]-[92]。CKD-aP 患者的这一传导通路可能存在多环节异常。研究发现, 与无瘙痒的 HD 患者相比, CKD-aP 患者的 T 型钙通道亚型 Cav3.2、大电导钙激活钾通道(big conductance calcium-activated potassium channel, BKCa)及钙激活氯离子通道(Anoctamin 1, ANO1, 又称跨膜蛋白 16A, Transmembrane protein 16A, TMEM16A)的表达显著上调, 而瞬时受体电位通道香草酸亚型 1 (Transient receptor potential vanilloid 1, TRPV1)的表达下降[93]。这种特定离子通道的表达谱改变可能共同导致神经元兴奋性增高。同时, B 型钠尿肽(B-type Natriuretic Peptide, BNP)已被认为是存在于小鼠瘙痒感受神经元中的一种瘙痒选择性神经肽, 主要在 TRPV1 神经元中表达, 而 TRPV1 的体感神经元能够触发瘙痒, 提示 BNP 与特定瘙痒神经元亚群密切相关[94] [95]。此外, 神经生长因子-4 (Neurotrophin-4, NT-4)在 CKD-aP 患者血清中水平升高并与瘙痒程度正相关, 提示其可能参与瘙痒的神经调节[96]。表皮瘙痒的激活可能还与多种神经递质有关, 包括血清素、降钙素基因相

关肽、阿片肽、组胺和其他细胞因子[97]。MHD 患者常合并感觉异常和不宁腿综合征, 其 CKD-aP 的发生率显著增高; 反之, CKD-aP 患者中周围感觉运动神经病变和自主神经异常的患病率也显著增高, 提示这些神经功能障碍与瘙痒可能存在共同的病理生理基础或相互促进的临床关系[98]-[100]。在富含腺嘌呤饮食诱导的 CKD 小鼠模型中, 氧化应激、全身性炎症和线粒体功能障碍被认为是神经变性和神经功能紊乱的根本原因, 从而诱发神经性疼痛和病理性瘙痒[97][101][102]。加巴喷丁、普瑞巴林、辣椒素等治疗神经性疼痛的药物, 能有效缓解部分 CKD-aP 患者的症状, 为神经系统机制提供了有力的临床佐证[98][103]-[106]。

4. 总结与展望

CKD-aP 的发病机制复杂, 涉及多方面相互作用, 可能是一个由尿毒症毒素累积启动, 涉及皮肤屏障、免疫炎症、阿片系统及神经通路等多系统深度交互形成的复杂网络, 各系统共同驱动瘙痒的发生与持续。值得注意的是, CKD-aP 的临床表现存在显著的异质性, 其发病率、严重程度及治疗反应在个体间差异显著, 且与多种因素的关联性在不同研究中常不一致。这种异质性强烈提示, CKD-aP 并非单一的疾病实体, 而是在尿毒症这一共同背景下, 由不同主导病理机制与个体遗传、环境、共病等因素相互修饰, 所呈现出的多样化临床表型。

因此, 未来的研究需超越对单一机制的孤立关注, 应致力于揭示这些机制的交织关系, 在系统层面揭示这些通路之间的动态交互网络与关键节点, 结合多组学技术与临床表型, 寻找能够区分不同主导机制类型的特异性生物标志物, 进而探索基于病理生理机制的临床分型, 为开发针对性治疗策略、实现个体化医疗提供坚实的理论依据, 最终改善终末期肾病患者的长期生活质量与预后。

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