Advances in Clinical Medicine 临床医学进展, 2022, 12(5), 3777-3786
Published Online May 2022 in Hans. http://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2022.125545

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慢性肾脏病患者脑卒中的发生机制及治疗进展

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收稿日期：2022年4月9日；录用日期：2022年5月3日；发布日期：2022年5月11日

摘　要

慢性肾脏病(Chronic kidney disease, CKD)已成为快速增长的全球健康问题，而CKD患者脑血管疾病所致的负担引起越来越多的关注。因CKD患者卒中后预后更差、死亡率更高，为肾脏病和神经科医师的临床工作增加了更大的挑战。本文就CKD和脑卒中的关系作以下综述。

关键词

慢性肾脏病，卒中，发生机制，治疗

Mechanisms and Treatment Progress of Stroke in Patients with Chronic Kidney Disease

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Received: Apr. 9th, 2022; accepted: May 3rd, 2022; published: May 11th, 2022

Abstract

Chronic kidney disease (CKD) has become a rapidly growing global health problem, and the burden of cerebrovascular disease in patients with CKD has attracted increasing attention. The poorer prognosis and higher mortality after stroke in patients with CKD have added greater challenges to the clinical work of nephrologists and neurologists. This article reviews the relationship between CKD and stroke as follows.

文章引用: 刘佩, 钟玲. 慢性肾脏病患者脑卒中的发生机制及治疗进展[J]. 临床医学进展, 2022, 12(5): 3777-3786.
DOI: 10.12677/acm.2022.125545

Keywords

Chronic Kidney Disease, Stroke, Mechanisms, Treatment

1. 引言

根据全球疾病负担研究，CKD 的发病率和死亡率随着人口老龄化的增长而增加，相关的代谢危险因素也呈现出上升趋势[1]。多数 CKD 患者死于 CKD 引起的心血管疾病(包括中风)而不是终末期肾病(End-stage renal disease, ESRD)本身[2] [3] [4] [5]。因此人们越来越关注 CKD 患者心脏并发症和脑血管疾病的高发病率，本文就肾功能不全对脑卒中影响的研究现状进行综述。

2. CKD 与脑卒中的关系

2.1. 流行病学

脑血管疾病和卒中在 CKD 的所有阶段都很常见，即使在早期 CKD 患者中，包括白质病变、隐性梗死和脑萎缩等在内的大脑病变也比普通(非 CKD)人群更多见[6]。在 CKD 患者中，卒中是第三大死亡原因，ESRD 患者因缺血性和出血性卒中住院的风险高出 10 倍[7] [8]。CKD 和卒中有许多共同的危险因素，如老年、糖尿病和高血压。而且已有越来越多的研究证明，CKD 中肾小球滤过率(Glomerular filtration rate, GFR)的降低及蛋白尿的存在是卒中包括缺血性和出血性卒中的独立危险因素[6] [9] [10] [11]。

2.1.1. GFR 的降低与卒中

低估算的肾小球滤过率(estimated glomerular filtration rate, eGFR)是否是独立于传统心血管危险因素的卒中危险因素，存在相互矛盾的流行病学证据。在对来自四项基于人群的纵向研究的荟萃分析中，eGFR < 60 mL/min/1.73m^2 的人群卒中发病率(10.3/1000)高于 eGFR ≥ 60 mL/min/1.73m^2 的人群(3.4/1000)。但调整传统的心血管危险因素后，这种有较低 eGFR 的卒中超额风险在统计学上并不显着差异(风险比[HR] 1.17，95% CI 0.95~1.44)。也有认为这种风险相关性的衰减是统计能力不足的结果[12]。相反的，在此之后的一项对 33 项前瞻性研究和对 83 项研究进行大型荟萃分析发现低 eGFR 与卒中风险独立相关[13] [14]。在韩国进行的一项全国性的回顾性队列研究也发现，在调整多个传统危险因素后，缺血性卒中的风险随着 eGFR 的降低男性增加，出血性卒中风险男女之间没有显著的关系[15]。因此 GRF 与卒中的相关性仍需要更多的研究来进一步证明。

2.1.2. 蛋白尿与卒中

蛋白尿已被证实和卒中之间有强且独立的关系。在对 140,231 人的 10 项前瞻性队列研究的荟萃分析发现，蛋白尿患者与无蛋白尿的患者相比，卒中风险增加了 71%。调整了已知的心血管危险因素后，即使蛋白尿和卒中之间的关系减弱了 30%，蛋白尿所致的额外卒中风险仍具有统计学意义(RR, 2.81 [95% CI, 1.78 to 4.42] vs RR, 1.94 [95% CI, 1.37 to 2.75]) [16]。近期近 200 万名有超过 26,000 起中风事件的参与因素进行的荟萃分析得出：蛋白尿是中风的风险[17]。在一项 meta 分析中，与微量白蛋白尿患者相比(RR 1.58, 95% CI 1.39~1.80)，大量白蛋白尿患者发生卒中的风险更高(RR 2.65, 95% CI 2.25~3.14) [18]。在一项中风

地理和种族差异(REGARDS)的全国性队列研究中发现，蛋白尿增加卒中风险的程度与种族差异有关：在黑人中，较高的尿白蛋白/肌酐比值(urinary albumin to creatinine ratio, UACR)与卒中风险相关，且独立于传统风险因素和 eGFR，而在白人中这种关联不明显[19]。

2.1.3. 透析与卒中

透析会增加卒中的风险。早在 20 世纪 90 年代即报道透析患者中出血性卒中的发生率高于缺血性卒中。在一项日本的前瞻性研究发现，维持性透析患者较普通人群，卒中的相对风险为 5.2，脑梗死为 2.0，脑出血为 10.7 [20]。后续的研究也证明透析治疗的 ESRD 患者发生脑卒中的风险是一般人群的 4~10 倍，尤其第一年透析的脑卒中风险显著增加[7] [8] [21]。大约三分之二的 75 岁以上的透析患者将在中风后一年内死亡[22]。除此之外，CKD 和 ESRD 患者往往遭受功能预后更差、发病率和死亡率更高的中风[6] [23] [24] [25]。Kumai 等人对来自日本多个卒中中心登记处的 3778 名首次发生缺血性脑卒中的研究发现，CKD 患者入院时的 NIHSS 评分明显高于非 CKD 患者。在调整了可疑的混杂因素后，CKD 患者住院期间 NIHSS 评分增加≥2 分的风险增加 49%，住院死亡率增加 138% [23]。在对 232,236 患者的队列研究发现，即使在调整了合并症和初始 NIHSS 评分，eGFR < 15 mL/min/1.73m^2 未透析患者，急性缺血性卒中后住院死亡的风险也比肾功能正常的患者高 2.5 倍[24]。在有脑出血(intracerebral hemorrhage, ICH)患者中，与无肾功能损害的患者相比，eGFR < 45 mL/min/1.73m^2 的患者血肿体积增加 3 倍，死亡风险增加 4 倍[26]。其可能的机制有以下几方面。

2.2. CKD 合并脑卒中的发生机制

2.2.1. 脑血管病与肾脏疾病相似的解剖学结构

肾脏和大脑对血管损伤具有独特的易感性，这两个器官的微血管调节在解剖学和功能上相似：都是高血流量，依赖于局部的自我调节。“应变血管假说”被认为是 CKD 和中风之间关联的可能机制。髓旁肾单位的肾小球传入小动脉和大脑穿孔动脉都是由大的高压动脉直接产生的小而短的血管。当动脉暴露在高压下，必须保持强烈的血管张力，在短距离内提供一个较大的压力梯度[27]。这种血管被称为“应变血管”，极易发生内皮功能障碍和脂质透明变性，与肾小动脉硬化类似，脑血管中形成脂质透明变性，这是腔隙性卒中的一个特征性发现。脂质透明变性损害大脑自身调节，减少局部脑血流，导致这些皮质下穿孔动脉供应区域的缺血性或出血性卒中发生率较高[28] [29]。因此微量白蛋白尿反映了近髓肾单位入球小动脉的损伤，也是脑小血管损伤的早期标志[30] [31]。

2.2.2. CKD 患者中慢性炎症、氧化应激与内皮功能障碍对卒中的影响

CKD 患者各阶段均存在慢性微炎症。在 CKD 早期，血液中的促炎因子 IL-6、TNF-a、骨保护素、骨钙素、骨桥蛋白和成纤维细胞生长因子 23 水平(fibroblast growth factor-23, FGF-23)明显升高[32] [33] [34]。在中晚期 CKD 患者中上述炎症因子是临床不良结局和死亡的有力预测因子[35]。尿毒症毒素能促进巨噬细胞向有害的促炎性 M1 表型转化，并激活小胶质细胞以促进脑卒中后脑损伤发生，也能促进 CKD 患者中的氧化应激和内皮功能障碍[36] [37]。内皮细胞产生的舒血管物质一氧化氮(NO)，前列环素和超极化松弛因子减少，而且减少抑制血小板聚集、平滑肌细胞增殖、单核细胞黏附和黏附分子的表达，血管壁易受动脉粥样硬化和血栓形成的影响[38]。以氧化应激诱导的 NO 利用降低为特征的内皮功能障碍被认为是动脉粥样硬化发病机制的早期事件[39]，也是导致 CKD 患者动脉硬化和动脉僵硬的重要因素[40]。多种因素如高同型半胱氨酸血症、尿毒症毒素等可通过增加氧化应激加重动脉僵硬[39] [41]。从而损害血脑屏障(blood-brain barrier, BBB)的完整性并促进白细胞浸润，促进尿毒症毒素进入中枢神经系统[42]。在肾脏远端肾小管中表达代表的 Klotho 蛋白是 FGF-23 的核心受体，调节钙和磷的代谢以及维持内皮和血管平

滑肌细胞功能。随着 CKD 的进展，Klotho 蛋白表达降低可能导致血管钙化和内皮功能障碍，可能导致卒中发生[43] [44]。

2.2.3. CKD 患者的动脉硬化和血管钙化

CKD 患者中慢性炎症、氧化应激、内皮功能障碍、尿毒症毒素、钙磷代谢失调等因素已被证实可加速全身血管的动脉硬化及血管钙化[40] [41] [43] [45] [46] [47]。在晚期 CKD 患者中，高磷血症和继发性甲状旁腺功能亢进会导致骨吸收与形成障碍，阻止骨骼作为过量钙和磷的储存库，钙随之沉积在异位软组织部位，包括血管系统[48] [49]。另一方面，能抑制动脉壁钙化的内源性因素(包括 Klotho，基质谷氨酸蛋白，焦磷酸盐和胎球蛋白-A)在 CKD 患者中缺乏可能是加重血管钙化的另一重要原因[49] [50] [51]。肾功能不全的程度与颈动脉粥样硬化的程度有关，颈动脉粥样硬化既是未来心血管疾病发生的预测指标，也是大脑血栓直接来源。在一项横断面的研究显示，颈动脉内膜-中膜厚度(carotid intima-media thickness, CA-IMT)与肾功能呈负相关[10] [52]。在一项包含 3364 名参与者的社区队列研究中，多变量分析显示肾功能是 CA-IMT 增加、亚临床动脉粥样硬化进展以及致命和非致命性血管事件增加的有力预测因素，与传统和非传统心血管危险因素无关[53]。与此同时，肾功能下降与异质性斑块的显著增加有关，轻度肾功能异常也是异质性斑块的潜在独立危险因素[5] [54] [55]。一项基于“中国高血压调查”的横断面研究发现 CKD 与颅内动脉狭窄(intracranial artery stenosis, ICAS)相关，且这种相关性与后循环 ICAS 关系更密切[56]。

2.2.4. CKD 患者脑自身调节受损和脑血流改变

由于肾脏和大脑具有相似的微血管系统和血管调节，都由"低阻力"血管回路灌注，为保持收缩期和舒张期连续的高容量血流，脑血管系统显示出强大的自我调节能力，以尽量减少低血压状态下的低灌注和高血压状态下的高灌注[28] [57]。脑自身调节是一种复杂的内在调控机制，通过改变脑血管阻力以顺应血压、脑灌注压或代谢需求的变化来维持恒定的脑血流量[58] [59]。肾脏疾病通过损害脑自身调节、重塑脑血管系统和减少脑血流量而对卒中风险产生独特影响[57] [60]。CKD 患者血管透明样变替代小动脉平滑肌会增加血管壁僵硬，损害自身调节[28] [50]。一项针对急性缺血性卒中后患者的前瞻性研究发现，eGFR 降低的个体的大脑自我调节能力较差，并与缺血性卒中向出血性转化的风险增加相关，出血转化可能是由于自身调节受损的突破性高灌注和微血管损伤[61]。eGFR 降低和自身调节受损的结合降低了卒中后出现良好功能结局的可能性。灌注相关的脑损伤在肾脏疾病患者中可能更常见，尤其是接受透析治疗的患者。来自荷兰的一项创新研究对年龄 ≥65 岁的稳定血液透析患者在进行透析时进行了 3 次 PET-CT 扫描发现，在透析期间，所有大脑区域的脑血流量下降了 10% ± 15%，其中血流量从平均每分钟 34.5 ml/100g 下降到 30.5 ml/100g [62]。这种对本应稳定的、自身调节的脑血流的破坏被假设为使血液透析患者易患卒中的机制。

2.2.5. CKD 患者心房颤动与血栓形成

CKD 患者发生心房颤动(atrial fibrillation, AF)的风险较高[63] [64] [65]。晚期 CKD 患者的 AF 患病率为 4%~21%，透析患者为 7%~27%，这明显高于普通人群。反之，AF 的存在使 CKD 和 ESRD 患者都具有较高的卒中风险[65]。CKD 患者中 FGF23 升高与 AF 发生风险的增加独立相关。FGF-23 与左心室肥厚、心房扩大和心力衰竭事件发生有关[66]。CKD 与左心房血栓形成环境有关。在接受经食管超声心动图检查的非瓣膜性 AF 患者中血栓形成环境的患病率随着 eGFR 的下降而增加[5]。CKD 中受损的内皮细胞会释放异常的血栓形成和抗血栓形成介质，如组织因子、凝血因子 fVIII、血栓调节蛋白、内皮蛋白 c 受体和血管性血友病因子(vWF)，从而改变血液成分和血流动力学特性[67]。机体血流动力学变化随着肾功能不全的严重程度而加重，促进血栓形成、脑出血或混合脑血管事件。因此，有学者建议在血栓栓塞风险

预测评分中纳入肾功能的测量，包括 CHA2DS2-VASc 和 CHA2ds2-VAK 评分。CKD 患者房颤的高发病率所致的心源性栓塞及促血栓形成作用可能是其卒中风险增加的机制之一。

2.2.6. CKD 患者凝血系统功能障碍及抗凝药物

CKD 患者特别容易发生出血性卒中。出血性卒中风险增加的一个可能机制是脑微出血的易感性[68]。可能的机制是尿毒症改变了内皮细胞中的肌动蛋白骨架和紧密连接蛋白，使 CKD 患者容易发生微出血[69]。同时，透析时反复使用抗凝药物会增加脑微出血和脑出血的风险[70] [71]。一项评价 CKD 患者新型凝血和血小板功能测定方法的横断面研究发现，在 CKD5 期患者中，多电极聚集度测定法(multiple electrode aggregometry, MEA)检测患者二磷酸腺苷和凝血酶受体激活肽显著低于健康对照组，提示血小板聚集缺陷，而且 eGFR 是血小板功能障碍和高凝状态的独立决定因素[72]。

2.2.7. 遗传因素

CKD 的亚洲和西非人卒中的风险高于其他人种。亚洲血统的 3 期(或更高)CKD 患者的卒中风险显著增加。目前尚不清楚遗传(基因)、环境或这些因素的混合是否会促进风险[19] [73] [74] [75]。近期有研究报道，载脂蛋白 L1 基因(APOL1)与心血管疾病(CVD)的风险增加独立相关[76] [77]。在有非洲血统的患者中，APOL1 中的肾风险变异可能增加肾脏疾病和卒中的风险[74]。REGARDS 的亚组分析报告称，携带 APOL1 肾脏风险基因型(2 个 G1 和/或 G2 变异体)与小血管缺血性卒中独立相关[78]。近来发现载脂蛋白 E(APOE)、COL4A1 突变等与脑血管病风险增加有关[5]。因此有关遗传机制是否在 CKD 患者的卒中高风险中产生作用需要进一步探究。

3. CKD 患者脑卒中的治疗

CKD 和 ESRD 患者脑卒中的预防和管理由于风险和合并症的增加而变得困难和复杂。与一般人群相比，CKD 各阶段的中风后结局都较差。Dad 和 Weiner 等人[6]建议，对于不需要透析的 CKD 患者，卒中的预防和管理可以与普通人群的方法相似。包括已知的危险因素，如肥胖、高血压和糖尿病的管理，对降低卒中风险至关重要[79] [80]。改善 GFR 和减少蛋白尿的策略也有效降低该人群卒中的风险。对 CKD 1 期和 2 期患者可使用阿司匹林治疗，但在更高阶段是否使用仍存在争议[81]。对于 ESRD 患者，基于普通人群中风预防和管理的药物，如他汀类药物、抗血小板药物和华法林等，已被证明对 CKD 5 期患者的益处甚微，甚至可能造成损害[11]。ESRD 患者在急性中风的情况下需积极的治疗。在没有禁忌症的情况下，在最初 3 小时内出现的急性缺血性卒中患者以及在最初 4.5 小时内出现的多数患者应接受溶栓治疗[6]。组织型纤溶酶原激活剂(tPA)阿替普酶是急性缺血性卒中中研究最充分的溶栓剂。没有根据肾功能调整剂量，阿替普酶说明书指出使用的后出血风险在某些情况下可能会增加，包括“严重肾病”[6] [82]。有研究回顾了 7168 名急性卒中患者使用组织纤溶酶原激活剂的数据，其中 28%患有 CKD。CKD 患者发生脑出血的风险增加，并且在 3 个月时更有可能出现较差的预后[83]。出于安全考虑，大型临床试验通常排除了晚期肾功能不全和透析的患者。因此，溶栓治疗对合并肾功能不全的急性缺血性卒中患者的临床结果是有益还是有害仍存在争议。然而，近年来包括血栓切除术和支架置入术等血运重建和血管内设备的进展使动脉内治疗(intra-arterial therapy, IAT)成为一种有价值和有效的选择，通常与已建立的溶栓治疗相结合[6] [84]。目前 CKD 患者急性脑卒中最有效管理的证据仍然缺乏，目前针对卒中的治疗需根据个体患者的背景进行优化，改善此类患者预后及降低全球负担仍面临着巨大挑战[85]。

4. 讨论

CKD 和 ESRD 的患病率不断增加，卒中的风险也在增加，与一般人群相比，CKD 各个阶段的中风

后预后都较差。可能的机制包括氧化应激、慢性炎症、尿毒症、脑血流失调、血管钙化、动脉硬化、以及血液透析患者使用抗凝剂等。CKD 和 ESRD 患者脑卒中的预防和管理是复杂的。目前还没有针对 CKD 患者卒中的一级预防与治疗措施，由于治疗干预的风险和副作用增加，也缺乏高质量的大型随机对照试验来指导治疗。因此，迫切需要有效的无创筛查和一级预防工具，以尽量减少该人群卒中相关的发病率和死亡率。寻找新的有效靶点以及改善这类患者的预后应该是未来研究的主题。

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