·文献综述·

痛风和高尿酸血症与眼部疾病的研究进展

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摘要
痛风为一种系统性炎性疾病,是世界范围内最常见的关节炎之一,其中高尿酸血症是痛风发病的主要危险因素。痛风的发病机制包括尿酸盐结晶沉积继发炎症及氧化应激。而炎症及氧化应激正是多种眼病的发病机制。目前已有较多研究提示痛风和高尿酸血症与眼部疾病的相关性,包括尿酸盐结晶直接沉积在眼部结构、干眼、角膜内皮损伤、巩膜炎、葡萄膜炎、青光眼、年龄相关性黄斑变性、糖尿病视网膜病变,以及某些代谢性疾病如甲状腺相关眼病等。另外由于尿酸自身的抗氧化活性,尿酸水平还被认为与多种视神经病变如多发性硬化相关视神经炎、视神经脊髓炎等有关。尽管尿酸水平和眼部疾病的相关性已被报道,但仍存在许多问题亟待解决。为了更全面地了解痛风和高尿酸血症和眼部疾病的关系,文章将从发病机制、发病特点等逐一展开,以期提高对痛风和高尿酸血症的认识,并为将来相关研究提供参考。
关键词:痛风;高尿酸血症;尿酸;眼病
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Research progress of ocular diseases related to gout and hyperuricemia

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Abstract
• Gout is a systemic inflammatory disease and one of the most common forms of arthritis worldwide. Hyperuricemia is the leading risk factor for gout, with a high incidence rate. The etiology of gout involves the deposition of urate crystals, secondary inflammation, and oxidative stress. These inflammatory and oxidative stress contribute to the pathogenesis of a variety of ocular disorders. Numerous studies have found a correlation of gout and hyperuricemia with ocular diseases, such as direct urate crystal deposition in ocular structures, dry eye syndrome, corneal endothelial damage, scleritis, uveitis, glaucoma, age-related macular degeneration, diabetic retinopathy, and certain metabolic diseases like thyroid-related eye diseases. Furthermore, because of its antioxidant effect, uric acid levels have been linked to a variety of optic neuropathies, including multiple sclerosis-related optic neuritis and neuromyelitis optica. Although the correlation between uric acid levels and ocular diseases has been reported, many aspects remain unresolved. To gain a more thorough understanding of the association between gout, hyperuricemia, and ocular illnesses, this review will delve into their pathogenesis and disease characteristics, aiming to increase knowledge about gout and hyperuricemia and serving as a reference for future studies.
• KEYWORDS: gout; hyperuricemia; uric acid; ocular disease

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0 引言

痛风是世界范围内最常见的关节炎类型之一,且其发病率仍在不断增加。血清中的尿酸升高是痛风最主要的危险因素[1]。近年的研究及临床实践中发现痛风及高尿酸血症患者可出现不同程度的眼部病变,包括干眼[2]、角膜病变[3]、青光眼[4]、黄斑病变[5]等多种眼部疾病,尤其是近年来许多国内外学者以痛风及眼病为研究对象开展了一系列临床研究。基于此,本文将对痛风及高尿酸血症相关眼部疾病的国内外研究进行系统综述,以提高广大眼科医生对痛风及高尿酸血症患者眼部疾病的认识。

1 痛风及高尿酸血症

1.1 定义及流行病学 痛风是一种代谢性疾病,主要表现为疼痛性炎性关节炎,以下肢关节最易受累。痛风的发生与血清中尿酸(uric acid, UA)水平升高有关,当血清中的UA超过机体可代谢的阈值,即7 mg/L(420 μmol/L)则称为高尿酸血症[1]。随着血清中UA持续升高,尿酸钠盐结晶形成并沉积于关节、肌腱及组织中,从而激活机体固有免疫,从而导致痛风的发生[6]。高尿酸血症和痛风的共同危险因素包括食用嘌呤含量高的食物、饮酒、慢性肾病[1]、肥胖、糖尿病、血脂异常[7]等,另外利尿剂和环孢素等药物也可以增加痛风和高尿酸血症发生风险。

痛风的发病率在不同国家和地区间存在差异,以沿海国家及地区发病率较高,其中中国台湾土著及新西兰毛利

人发病率高达 10%[8],其次在南美洲及欧洲地区,发病率约 1%-4%[9],在我国大陆地区,痛风总体发病率约 1.1%[10],高尿酸血症发生率却高达 14%(2018 年),且其发生率正逐年增加。

1.2 病理机制 尿酸为人体内嘌呤代谢的终末产物,由黄嘌呤氧化还原酶催化黄嘌呤产生,尿酸在尿酸氧化酶的作用下可氧化分解为可溶性的尿囊素,并最终分解为葡萄糖和尿素[11]。由于人类缺乏尿酸氧化酶,导致尿酸无法分解,只能通过肾脏排泄,因而导致人类血清尿酸浓度较其他哺乳动物高[12]。在生理状态下,UA 可通过清除过氧自由基等发挥抗氧化作用,约占血浆抗氧化作用的 65%[13]。基于 UA 强大的抗氧化活性,UA 在缺氧再灌注损伤、急性卒中[14]、神经退行性病变[15]中发挥重要的神经保护作用。

然而在 UA 超过机体代谢能力时,可沉积形成尿酸盐结晶,激活体内固有免疫系统。单核细胞和巨噬细胞吞噬尿酸盐结晶后向 M1 表型发生极化[16],激活细胞内 NLRP3 炎症小体,引发促炎因子白介素 1β(interleukin,IL-1β)释放从而导致痛风急性炎症反应[1]。IL-1β 可招募中性粒细胞,促进多种细胞因子、趋化因子的释放及中性粒细胞胞外诱捕网(neutrophil extracellular traps,NETs)的形成[17-18]。随着病情进展,NETs 包裹尿酸盐结晶,逐渐降解趋化因子和细胞因子,进而疾病进入缓解期[19]。

尽管在生理状态下 UA 作为一种抗氧化剂发挥作用,但尿酸盐结晶形成导致上述炎症后可通过 IL-33 触发中性粒细胞释放大量活性氧[19],介导氧化应激反应,同时可以刺激位于背跟神经节的神经元细胞膜的瞬时受体电位 A1 通道,导致痛觉增强[20]。

痛风的发病复杂,了解尿酸代谢途径、疾病信号通路等有助于更好地理解痛风相关眼病的发生机制。

2 高尿酸血症相关眼部表现

2.1 眼表和角膜 尿酸盐结晶除沉积在关节外,还可能出现在眼表组织如结膜、角膜中。结膜下结晶主要见于长期痛风病史患者,可表现为结膜下簇状立方体结晶[21]、粉笔灰样物沉积[22],其周边结膜常无炎症表现。结膜下结晶在光镜下表现为多核巨细胞和周围组织细胞包裹的嗜酸性物质,电镜下表现为组织细胞吞噬的结晶,在细胞内及细胞外组织均可出现,该镜下表现与关节及软组织的痛风石表现相同[22]。除结膜外,尿酸结晶还可沉积于角膜上皮下及前弹力层,表现为带状角膜变性和角膜上皮下结晶[23]。

作为一种系统性免疫代谢疾病,同其他系统性疾病如糖尿病、干燥综合征、系统性红斑狼疮一样可导致干眼。一项大规模横断面研究显示,痛风与干眼的发生呈显著正相关,痛风患者中干眼的发病率为 9.1%,显著高于对照组[2]。在长期痛风的患者中,干眼发生的主要危险因素包括视频终端产品的使用及饮酒[24]。研究显示血尿酸水平与系统性红斑狼疮患者的新发损伤显著相关[25]。且血尿酸水平升高可以增加干燥综合征患者高血压及心血管疾病的发生风险[26-27]。然而目前尚无相关研究表明痛风及高尿酸血症可增加干燥综合征及系统性红斑狼疮患者干眼的发生风险。痛风及高尿酸血症导致干眼的机制推测与局部炎症及氧化应激有关,痛风发病的一系列炎症反应可导致包括 IL-1β、肿瘤坏死因子 α(tumor necrosis factor α,TNF-α)、基质金属蛋白酶 9(matrix metalloproteinase 9,MMP-9)等一系列促炎因子及细胞因子的升高,而这些炎症因子被认为在干眼的发病中发挥重要作用[28-29]。且目前已有研究证实痛风及高尿酸血症患者泪液尿酸水平显著增加,且泪液尿酸水平与泪液 IL-1β 水平显著相关[30]。

痛风及高尿酸血症可累及肾脏,通过线粒体钙过载介导氧化应激,从而损伤肾小球内皮细胞[31-32]。同样的,房水中的尿酸也可以对角膜内皮细胞产生损伤。研究表明,在痛风患者中角膜内皮细胞密度及六边形细胞比例显著低于正常,而中央角膜厚度显著增加[33],提示房水内的尿酸可损伤角膜内皮细胞,破坏其屏障功能从而导致角膜水肿。另外一项回顾性研究显示,痛风及高尿酸血症患者常规白内障超声乳化术后角膜内皮细胞丢失率高于正常对照[3]。这些研究表明尿酸可以直接损伤角膜内皮细胞,但是尚无相关研究阐述发病机制,推测可能与房水尿酸损伤角膜内皮细胞的 Na^+-K^+-ATP 酶有关[34],尿酸对角膜内皮损伤的具体机制及发病特点尚未完全阐明,房水中尿酸水平与角膜内皮损伤程度是否直接相关有待进一步研究。

2.2 巩膜和葡萄膜 血清尿酸除易沉积为结晶外,还可通过血流累及富含血管的巩膜及葡萄膜组织。早在 1936 年,就曾有文章报道痛风相关的表层巩膜炎、巩膜炎及虹膜睫状体炎,可表现为眼痛或无眼痛、球结膜水肿、混合充血、前房炎症等,且病程特点主要表现为反复发作[35]。痛风相关虹膜炎可急性发病,持续 2-3 wk 后快速缓解,在缓解期可不表现为任何异常或仅出现轻度虹膜后黏连[36],并且随着痛风治疗好转,虹膜炎可逐渐恢复[37]。

葡萄膜炎通常与自身免疫性疾病相关,眼内 TNF-α、IL-6 等炎症因子的水平升高都可能诱发葡萄膜炎的发生[38],因此痛风发病过程中可能通过上调炎症反应介导葡萄膜炎的发生。早在 1968 年 Killen[37] 曾经报道过 1 例痛风相关葡萄膜炎的患者,该患者为双眼全葡萄膜炎,在经历长期全身激素及免疫抑制治疗后无明显好转,在确诊痛风后加用降尿酸治疗后葡萄膜炎逐渐缓解。Singh 等[39]的研究显示,在美国患有痛风的老年人群发生葡萄膜炎的风险是对照组老年人的 1.53 倍。另外,葡萄膜炎可作为脊柱关节炎(spondyloarthritis, SpA)如强直性脊柱炎、中轴型脊柱关节炎等的眼部表现。脊柱关节炎为慢性炎症性疾病,研究显示合并葡萄膜炎的 SpA 患者疾病活动性及延迟诊断率显著高于不合并葡萄膜炎的 SpA 患者[40]。而研究已表明血清尿酸水平与 SpA 的疾病活动性显著正相关,因此推测尿酸参与 SpA 相关葡萄膜炎的发生。

2.3 青光眼 除角膜及眼表外,尿酸盐结晶还被发现沉积于虹膜表面及前房内,导致高眼压和角膜内皮失代偿[41]。虽然既往已有报道高尿酸导致青光眼的病例,但是目前对于尿酸与青光眼的关系仍然存在争议。国内有研究显示血清尿酸水平与原发性开角型青光眼(primary open-angle glaucoma,POAG)的发生呈负相关[4]。同样的,该团队的研究发现在原发性闭角型青光眼(primary angle-closure glaucoma, PACG)患者血清尿酸水平显著低于对照组[42],且处于青光眼进展期患者的血清尿酸显著低于非进展期青光眼患者[43]。该研究认为尿酸作为一种抗氧化剂具有神经保护作用。且一项大样本的研究显示痛风的病史可显著降低 POAG 的发生风险,而单纯的高尿酸血症却与青光眼发生无显著相关性[44]。然而,国外有研究显示在 POAG 和正常眼压青光眼(normal-tension glaucoma,NTG)中血清尿酸显著高于正常对照[45]。基于上述矛盾的结

果,Mohammadi 等[46]进行了一项荟萃分析以明确尿酸与青光眼的关系,共纳入 6 组研究,结果显示青光眼患者血清尿酸高于对照组,但无统计学差异。导致这种结果可能与入组研究过少,且未进行亚组分析有关,并且上述研究中患者血清 UA 均在正常范围内。另外有研究发现在缺血性视神经病变患者中血清尿酸水平作为一种氧化应激指标与眼压呈现显著正相关[47]。因此,尿酸与青光眼的确切关系及作用机制仍未明确,未来仍需大样本的数据探讨尿酸在不同类型青光眼中发挥作用。

2.4 视网膜和视神经 视网膜富含血管,因此与全身病密切相关,并常作为许多全身代谢性疾病如糖尿病、高血压、动脉硬化等的早期病变部位。尽管尿酸是重要的抗氧化剂之一,但是过高的血清尿酸可导致炎症反应,激活炎症细胞产生氧自由基,进一步导致氧化应激[48]。研究显示高尿酸水平可显著降低黄斑区脉络膜和内丛状层的厚度,推测高尿酸引起氧化应激及炎症从而损伤脉络膜血管内皮细胞和神经节细胞,损伤内、外血-视网膜屏障,最终导致黄斑区视网膜退行性改变[49]。并且一项来自中国南方的前瞻性临床研究已证实随着血清尿酸水平的增加,中央凹旁浅层血管密度显著降低,并出现脉络膜毛细血管血流不足,且这种相关性在女性患者中更为显著[50]。另外一项来自中国北方的研究中显示尿酸水平增加与视网膜毛细血管密度呈显著负相关,而这种相关性仅在男性中出现[51]。因此高尿酸血症可通过血管收缩、炎症反应、氧化应激等最终导致视网膜-脉络膜微循环异常从而导致多种视网膜及脉络膜疾病的发生。在多种视网膜疾病中,年龄相关性黄斑变性(age-related macular degeneration, ARMD)与痛风和高尿酸血症的相关性逐渐得到证实[52]。研究显示痛风患者中 ARMD 的每千人年发病率为 20.1,较对照组(11.7)显著增加[5]。另外一项回顾性研究显示在痛风发病率较高的中国台湾地区,痛风患者发生 ARMD 的风险比为 1.55[53]。除 ARMD 外,血清尿酸水平还与糖尿病视网膜病变(diabetic retinopathy, DR)的严重程度有关[54]。一项日本的前瞻性研究显示,高尿酸血症显著增加男性糖尿病患者发生 DR 的风险[55]。并且 DR 患者玻璃体腔内 UA 水平显著高于正常对照,且在增殖性 DR 中玻璃体 UA 显著高于非增殖性 DR[56]。另外对于糖尿病性黄斑水肿接受贝伐单抗玻璃体腔注射的患者,血清尿酸与术后视力预后呈负相关,提示血清尿酸可以成为黄斑水肿玻璃体腔注药术后视力预后的一个预测指标[57]。这些研究意味着血清及玻璃体尿酸水平有可能成为预测糖尿病患者 DR 发生、病程进展及视力预后的标志物之一。另外,痛风及高尿酸血症被认为与高血压性视网膜病变的发病显著相关,研究显示在患有高血压的女性患者中,尿酸每升高 10 mg/L 发生高血压性视网膜病变的风险增加 26%[58]。

鉴于尿酸的神经保护作用,痛风还被认为与视神经病变的发生有关。特发性脱髓鞘性视神经炎(idiopathic demyelinating opticneuritis,IDON)是视神经炎最常见的类型,常发生于多发性硬化(multiple sclerosis,MS)患者。过氧亚硝基阴离子是 MS 发病的重要氧化损伤物质,而正常水平的尿酸可抑制过氧亚硝基阴离子的发生从而产生抗氧化作用。研究显示 MS 患者的血清尿酸水平较正常人显著降低[59],且在新发 ON 的 MS 患者中,血清尿酸水平显著低于正常对照[60]。除 MS-ON 外,在视神经脊髓炎(neuromyelitis optica,NMO)患者中同样检测到低于正常值的尿酸水平[61]。另外,Stevenson 等[62]报道一个 PAX2 基因突变的高尿酸家族,发现了家族成员均出现视神经发育不良伴视野缺损。较低的尿酸水平与视神经炎相关,那么高尿酸水平是否同样会导致视神经损伤?研究显示尿酸可激活 NLRP3 炎症级联反应触发 ROS 产生导致细胞焦亡,介导心肌的缺血再灌注损伤[63]。尽管低尿酸与视神经炎的相关性已得到证实,但目前尚无相关临床研究证明高尿酸与视神经损伤的关系。

2.5 眼附属器 除眼球外,尿酸盐也可沉积于眼睑。不同于关节痛风石,眼睑尿酸盐沉积主要表现为无痛性眼睑肿物[64-65]。Chu 等[66]报道 1 例发生在内眦部的痛风石,切除后病理检查显示为炎症细胞包裹的松针样结晶,根据其发生位置推测可能为始发于内眦韧带,并将韧带作为尿酸盐累积的支架。皮肤的痛风石并不罕见,可表现为皮肤下灰黄色、颗粒状、硬质白色粉笔灰样结节,有的还可表现为溃疡性,皮肤变薄发生破溃。皮肤痛风石在显微镜下表现为局部钙化、脂肪坏死、肉芽肿性炎症等[67]。另外,尿酸作为 ATP 代谢产物之一,被认为与某些代谢性疾病相关。研究显示痛风显著增加甲状腺功能亢进的发生风险,且显著增加女性患者甲状腺功能减退及桥本氏甲状腺炎的发生风险,然而高尿酸血症与甲状腺疾病无显著相关[68]。甲状腺相关眼病(thyroid-associated ophthalmopathy,TAO)为一种自身免疫性疾病,由细胞免疫、体液免疫及多种细胞因子介导的自身免疫反应,导致眼眶淋巴细胞和浆细胞浸润,眼眶成纤维细胞向脂肪细胞分化[69]。TAO 患者血清尿酸水平显著高于对照组,且经过甲泼尼龙冲击治疗后可降至正常值[70]。然而尿酸与 TAO 严重程度及预后的相关性尚无相关报道,有待进一步研究。

3 小结

综上所述,痛风和高尿酸血症可累及眼部多种部位,导致或加重多种眼部疾病的发生。尽管目前已有许多文献支持痛风和高尿酸血症与眼部疾病的相关性,但仍有许多发病机制及发病特点等问题未能阐明,将来仍有较大的研究空间。本文通过对痛风和高尿酸血症相关眼部疾病的国内外研究进行系统综述,以提高广大眼科医生对痛风和高尿酸血症患者眼部疾病的认识。

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