·文献综述·

圆锥角膜性别差异的研究进展

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摘要

圆锥角膜是一种青春期起病,以角膜中央或旁中央变薄呈锥形突出为特征的致盲性眼病。目前该病的病因尚不明确,其发生受到多基因遗传背景、环境暴露因素以及生物力学失代偿等多种因素的共同作用。近年来多项研究表明圆锥角膜在发生和发展过程中存在显著的性别差异。在流行病学层面,多数研究提示该病在男性群体中高发;在临床特征方面,男性患者往往起病更早,且角膜形态学恶化等疾病客观指标表现更为严重;在病理机制层面,性激素表达差异及遗传易感性差异在疾病进展中扮演了关键角色;这种差异也进一步影响了临床防治策略的制定,例如针对高危男性群体的早期预警筛查及个体化的角膜交联干预时机。文章旨在从流行病学、临床特征、防治措施以及病理机制等方面综述圆锥角膜中的性别差异,以期为未来临床诊疗工作提供参考与帮助。

关键词:圆锥角膜;性别差异;流行病学;性激素
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Research progress on gender differences of keratoconus

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Abstract

• Keratoconus is an adolescent-onset blinding eye disease characterized by the protrusion and thinning of the central or paracentral cornea. The cause of keratoconus remains unclear, though its onset and progression arise from a multifactorial interplay involving a polygenic background, environmental exposures, and biomechanical decompensation. Recent studies have demonstrated significant gender differences in the pathogenesis and progression of keratoconus. At the epidemiological level, most studies suggest that the disease shows a male predominance; in terms of clinical features, male patients tend to experience an earlier onset and present with more severe clinical phenotypes, such as more serious corneal morphological deterioration; at the pathological mechanism level, sex hormone expression differences and genetic susceptibility differences play a key role in disease progression; this difference further affects the formulation of clinical prevention and treatment strategies, such as early warning screening for high-risk male groups and individualized corneal cross-linking intervention timing. This article reviews gender differences in keratoconus from the perspectives of epidemiology, clinical characteristics, prevention and treatment, and pathological mechanisms, providing relevant references and insights for future clinical practice.

• KEYWORDS: keratoconus; gender differences; epidemiology; sex hormones

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0 引言

圆锥角膜(keratoconus, KC)是一种以角膜扩张、中央区角膜基质变薄、呈圆锥形突起及高度不规则近视散光为特征的致盲性眼病[1]。目前圆锥角膜的病因及发病机制尚不明确,其发生可能是多种因素共同作用的结果,如遗传因素、炎症反应、氧化应激及性激素等在圆锥角膜的发病机制中均有一定作用[2-4]。一项包括 715 万样本的全球荟萃分析显示该病全球患病率约为 1.38:1000[5],男女比例在(0.91-2.83):1 之间[6]。目前已有研究表明圆锥角膜患者在流行病学、临床特征、防治措施、激素水平及遗传易感性等方面存在性别差异[7-9],本文就圆锥角膜性别差异的研究进展进行综述,以期为阐明该病发病机制及其个体化防治提供参考。

1 不同性别圆锥角膜患者的流行病学差异

既往多项研究报道,圆锥角膜在流行病学方面存在性别差异,见表 1。一项来自沙特阿拉伯的研究发现男女

表 1 与圆锥角膜流行病学相关既往研究

文献	文题	地区	患者年龄[$\bar{x}\pm s/M(P_{25},P_{75})$,岁]	样本量(n)	男/女比值
[10]	Incidence and severity of keratoconus in Asir province, Saudi Arabia	沙特阿拉伯	18.5±3.8	125	0.69
[11]	Much higher prevalence of keratoconus than announced results of the Gutenberg Health Study (GHS)	德国	54.8±9.7	51	1.22
[12]	Prevalence and incidence of keratoconus in Norway: a nationwide register study	挪威	28.9(21.4,38.9)	9 832	2.70
[13]	Baseline findings in the retrospective digital computer analysis of keratoconus evolution (REDCAKE) project	8 个欧洲成员站点(德国、瑞士、荷兰、葡萄牙和以色列等)	26.6±6.6	906	2.64
[14]	Keratoconus clinical findings according to different classifications	伊朗	27.4±7.2	1 081	1.63
[5]	The prevalence and risk factors for keratoconus: a systematic review and meta-analysis	全球	20-40	7 158 241	0.91-2.83
[15]	Age - specific incidence and prevalence of keratoconus: a nationwide registration study	荷兰	28.3±12.6	218	1.53
[16]	Keratoconus clinical findings according to different age and gender groups	土耳其	28.1±9.4	248	1.61
[17]	A hospital - based study on clinical data, demographic data and visual function of keratoconus patients in Central China	中国	22.1±6.3	307	2.66
[18]	Distribution of pediatric keratoconus by different age and gender groups	中国	15.1±2.1	446	3.80
[6]	Risk factors and severity of keratoconus on the East Coast of China	中国	23.3±6.4	391	2.83
[21]	Predictors of progression in untreated keratoconus: a Save Sight Keratoconus Registry study	澳大利亚	32.3±12.6	2 283	2.25
[22]	The Dundee University Scottish Keratoconus study: demographics, corneal signs, associated diseases, and eye rubbing	苏格兰	36.8±13.1	200	1.67
[23]	Predictive accuracy of the ABCD progression display among patients with keratoconus: a historic cohort analysis	以色列	34.5±13.6	293	1.66
[24]	Medium to long term follow up study of the efficacy of cessation of eye - rubbing to halt progression of keratoconus	法国	23.9±7.6	77	3.05
[25]	The association between sociodemographic factors, common systemic diseases, and keratoconus	美国	43.4±18.6	16 053	1.43
[26]	Clinical, demographic, and tomographic aspects related to iris mammillations among patients with keratoconus: a cross-sectional study	巴西	18(14,24)	106	0.93
[27]	Socioeconomic correlates of keratoconus severity and progression	美国	40.2±16.3	1 038	1.86
[28]	Risk factors and association with severity of keratoconus: the Australian study of Keratoconus	澳大利亚	36.4±14.2	260	1.41
[29]	Keratoconus in pre-teen children: Demographics and clinical profile	澳大利亚	10.8±1.4	294	2.34
[30]	Personalized model to predict keratoconus progression from demographic, topographic, and genetic data	英国	32.1±13.4	4 823	2.03

续表 1 与圆锥角膜流行病学相关既往研究

文献	文题	地区	患者年龄[$\bar{x}\pm s/M(P_{25},P_{75})$,岁]	样本量(n)	男/女比值
[31]	The sociodemographic and risk factors for keratoconus: nationwide matched case - control study in Taiwan, 1998-2015	中国台湾	36.1±15.8	5 055	1.45
[32]	Prognostic factors for the progression of keratoconus	英国	28.3±9.7	2 723	1.92
[33]	Association of genetic variation with keratoconus	澳大利亚、美国	38.3±14.3	116	1.69
[34]	Characteristics of keratoconus patients at a tertiary eye center in India	印度	21.4±6.7	274	2.22
[35]	A nationwide population - based study of social demographic factors, associated diseases and mortality of keratoconus patients in Denmark from 1977 to 2015	丹麦	32.0(24.0,44.0)	2 679	2.01
[36]	Keratoconus international consortium (KIC) - advancing keratoconus research	澳大利亚、美国、英国等 13 个国家	34.7±13.2	1 130	1.56
[7]	Differences in keratoconus as a function of gender	美国	39.3±11.0	1 209	1.32
[37]	The Aotearoa research into keratoconus study: geographic distribution, demographics, and clinical characteristics of keratoconus in New Zealand	新西兰	34.8±14.2	1 869	1.30
[38]	Artificial intelligence - based stratification of demographic, ocular surface high - risk factors in progression of keratoconus	印度	24.6±6.8	450	1.13
[39]	Prevalence and risk factors of keratoconus (including oxidative stress biomarkers) in a cohort study of Shiraz university of medical science employees in Iran	伊朗	43.2±5.8	39	0.63
[40]	Prevalence and incidence of keratoconus in South Korea: a nationwide population-based study	韩国	34.0(22.0,52.0)	1 552	0.78
[41]	Demographics of patients older than 50 years with keratoconus	美国	60.2±8.4	279	1.04

患者比例为 51:74,以女性患者为主[10]。同样有报道称圆锥角膜患者中男女患病率无明显差别[11],然而更多的国际与国内队列研究报道称男性患病率高于女性。一项基于挪威人群的研究调查了全国圆锥角膜患病率,最终共登记 9 832 例圆锥角膜患者,表明圆锥角膜的患病率为 192.08/100 000(95%*CI*:188.32-195.00),其中男性患病率较高,占总人群的 73%[12]。另一项针对圆锥角膜的回顾性研究对 8 个中心的 906 例圆锥角膜患者进行了统计分析,结果发现研究人群中男女比例失衡,男女比高达 3:1[13]。伊朗的一项前瞻性横断面研究共纳入了 1 081 例圆锥角膜患者,发现男女患者比例为 62:38,其中女性患者较男性患者更年轻[14]。一项来自荷兰 440 万人口的队列研究表明,在确诊的圆锥角膜患者中男性占 60.6%[15]。另一项来自土耳其的研究发现在 248 例圆锥角膜患者中,男性患者占总人群的 61.6%,女性患者占总人群的 38.3%[16]。

在中国圆锥角膜相关研究中,圆锥角膜在流行病学方面的性别差异及男性倾向则更为明显。一项针对中国中部圆锥角膜患者的研究指出男女比为 223:84[17];另一项针对中国儿童圆锥角膜患者研究同样指出男性占比高于女性(353:93),并且男女比例随着年龄的增长而下降[18]。来自中国西部、北部及东海沿岸人群的研究,同样发现男女患者比例极度不平衡[6,19-20]。上述流行病学数据的争议,可能不仅源于种族与地理环境差异,还与特定地区(如征兵体检群体)的筛查偏倚有关。

2 不同性别圆锥角膜患者的临床特征差异

越来越多的研究表明,圆锥角膜在疾病症状及进展方面存在性别差异。Fink 等[9]对 1 209 例圆锥角膜患者临床特征进行评估及分析,发现不同性别圆锥角膜患者的病史、眼部症状及体征存在差异:男性发病时间更早,病程更快,更倾向于选择手术干预;男性更可能出现 Vogt 纹;女性经常伴有眼部干燥和瘙痒的症状,并且在瘙痒、烧灼感、发红和干燥的症状方面的评分高于男性。Yang 等[18]研究发现男性患者的最佳矫正远视力、角膜前表面最大曲率值及平均屈光力差值高于女性患者,且角膜地形图圆锥角膜分级(topographic keratoconus classification,TKC)分期在男性和女性患者之间的分布存在明显差异,发现男性比女性更早发病并且更容易进展。一项针对中国东海沿岸人群的研究指出男性圆锥角膜患者急性水肿的风险增加,且男性患者病情更严重[6]。但既往有报道称女性圆锥患者病

情更重, Ramdas 等[42]分析了来自荷兰三个医疗中心的218 例 378 眼圆锥角膜患者的角膜地形图,发现女性的角膜曲率往往比男性高。上述证据表明,男性患者在客观指标上往往病情更重、进展更快,而女性患者在主观症状及部分特定体征上表现更为突出。这提示临床在评估不同性别患者时,不能采用单一标准,而需结合主客观指标综合判断。

3 圆锥角膜在防治措施上的性别差异

临床特征的性别差异直接影响了患者的干预时机与治疗结局。在手术干预方面,由于男性往往具有更高的进展风险,其接受终末期手术的年龄更早。Magalhaes 等[43]通过对 1 284 例 1 530 眼因圆锥角膜行角膜移植术的患者分析发现,共有 839 例男性患者(65.4%)因圆锥角膜接受了角膜移植术,平均年龄为 30.3±12.2 岁,445 例行角膜移植术的女性患者(34.6%)平均年龄为 34.5±14.8 岁,差异均具有统计学意义($P\leq0.01$),表明圆锥角膜中男性患者行角膜移植术的年龄更小,比例也更高。此外,后续随访研究发现,男性移植失败的风险同样显著增加。而女性接受深板层角膜移植术的比例明显更高。Yang 等[44]对圆锥角膜患者揉眼干预情况进行随访,发现干预成功组(基线揉眼但随访期间揉眼干预成功)和干预失败组(基线和随访期间均揉眼干预失败)之间男女患者比例无显著差异($P=0.90$)。近年来,角膜胶原交联术(corneal collagen cross-linking, CXL)已成为治疗圆锥角膜的重要手段。然而,关于 CXL 在不同性别患者中的疗效和术后反应的研究相对较少。Aljaberi 等[45]报道了在接受治疗(包含了手术与非手术治疗)的圆锥角膜患者中,女性更倾向于接受非手术治疗(如硬性透气性角膜接触镜或巩膜镜),且在随访时的主观生活质量优于男性,这一结果可能与非手术干预本身具有较低的医疗风险有关。目前关于 CXL 术后角膜生物力学是否存在性别差异,仍缺乏大样本的对比数据,需要未来进一步探讨。

4 圆锥角膜性别差异的潜在机制

圆锥角膜的性别差异可能与男女两性在社会行为习惯及环境暴露方面的差异有关[7,18]。Weng 等[46]通过对特应性角结膜炎的回顾性研究,发现在 7 a 随访时间里,特应性角结膜炎患者的圆锥角膜发病率是对照组的 2.49 倍,且男性患者可能存在更剧烈、频繁的揉眼。Di Zazzo 等[47]发现过敏性结膜炎患者中男性患者占比较高,且随年龄增长男女比逐渐下降。一项中国圆锥角膜专病队列的研究发现儿童圆锥角膜患者男性占比更高,随着年龄的增长,男女比例呈逐年下降的趋势,这一趋势与圆锥角膜中男女比趋势变化一致,提示炎症反应可能与圆锥角膜中的性别差异存在密切关联。

圆锥角膜的性别差异还可能与性激素水平相关[48]。近年来多项研究阐明了性激素对角膜的病理生理影响及其在圆锥角膜中的作用[49-50]。既往研究发现,在性激素发生变化的时期(如妊娠期、摄入外源性激素等),圆锥角膜存在进展的风险[51-53]。Wickham 等[54]通过对不同组织中雄激素、雌激素和孕酮受体的 mRNA 检测发现,雌激素、雄激素及孕激素受体广泛分布于眼内的各个部位:泪腺、睑板腺、睑结膜和球结膜、角膜、虹膜和睫状体、晶状体、葡萄膜、脉络膜和视网膜,表明眼是雌激素、雄激素及孕激素作用的靶器官。此外,Suzuki 等[55]和 Nuzzi 等[56]研究也证实了性激素受体广泛分布于人类角膜上皮细胞、基质细胞、以及内皮细胞中,提示性激素可能通过与特异性受体结合,从而对角膜病理生理产生一定影响。Goto 等[57]通过对 100 例不同年龄正常人群的角膜地形图分析,发现角膜不规则性随着年龄的增长而增加,推测性激素水平的降低可能在角膜结构随年龄的性别相关变化中发挥作用,进一步佐证了性激素对角膜的生理变化的潜在影响。

多项研究证实了圆锥角膜患者性激素的改变。既往研究发现圆锥角膜患者角膜上皮中雄激素和雌激素受体的表达增加,而孕激素受体的表达显着降低[58-59]。此外,研究发现圆锥角膜患者的唾液和血浆雌三醇和雌酮水平下调,而硫酸脱氢表雄酮水平上调[60-62]。不仅如此,Karamichos 等[63]通过对 86 例圆锥角膜患者和 45 名健康对照血浆及角膜基质细胞中促性腺激素的检测分析,发现了圆锥角膜患者中促黄体生成素/促卵泡激素比例的改变,提示促性腺激素在圆锥角膜发病机制中可能存在作用。还有报道称女性性激素(特别是妊娠期的雌激素、孕激素、松弛素)通过改变角膜的结构、水合状态和生物力学特性,可能间接影响角膜敏感度[64]。这可能解释了为何女性角膜敏感度普遍高于男性[65],导致男女患者呈现出“主观症状与客观体征相分离”的现象。圆锥角膜好发于青春期,而青春期时两性体内性激素变化存在一定的性别差异[66-67],性激素可能通过促进眼部炎症因子及基质金属蛋白酶的产生[68-69],破坏角膜基质胶原蛋白网络结构导致圆锥角膜,同时性激素可能通过免疫相关途径引发圆锥角膜[68-69]。基于以上证据,我们认为圆锥角膜的性别差异与男女两性在青春期体内性激素变化差异有关。

圆锥角膜的性别差异也可能与遗传易感性相关。一项来自沙特的回顾性病例-对照研究发现,rs2371597 位点与圆锥角膜的相关性在不同性别中存在差异,CC 和 CG 基因型的男性患者发生圆锥角膜的风险更高,提示遗传易感性可能在圆锥角膜性别差异中也有重要作用[8]。目前,GWAS 揭示的遗传水平性别差异在青光眼[70]、高度近视[71]等其他眼科相关疾病中已有报道,但目前专门针对圆锥角膜进行性别分层的大样本 GWAS 研究仍然较为缺乏。未来仍需纳入更大样本量的多中心全基因组研究,以进一步探讨和阐明圆锥角膜遗传易感性在性别方面的具体差异。

值得注意的是,遗传因素与性激素网络并非孤立存在,二者在圆锥角膜的发病中存在深度的交互作用。研究发现,男女患者在角膜病变过程中启动了截然不同的基因途径:男性的角膜变薄主要受雄激素相关通路的驱动,而女性的病变则更多与免疫反应及激素调节功能的减弱有关[72]。同时,研究还发现了仅在女性患者中特异性表达的表观遗传调控网络[72]。这些分子层面的直接证据表明,男女圆锥角膜患者不仅在临床表现上不同,其深层的致病通路也存在本质区别。

5 总结与展望

圆锥角膜作为一种多因素致盲性眼病,其在流行病学、临床表型及发病机制上的性别差异已得到大量循证医学支持。目前已达成共识的是:在大多数地区,男性患病率更高、发病年龄更早且病情客观指标更严重[9,13,40,44],而女性则表现出更突出的主观症状[9,45];性激素受体在角膜组织中的广泛存在及表达失衡,是解释这些性别差异的核心生物学基础[51]。然而尚存争议与未解决的问题在于:

不同地区流行病学数据的矛盾究竟是完全由遗传背景导致,还是存在特定人群的筛查偏倚。例如在国内临床实践中,大量无症状的圆锥角膜患者是在参军入伍目的驱动下,于屈光手术术前筛查(如角膜地形图检查)时被偶然确诊的。由于男性群体出于此类目的寻求近视激光手术的比例相对较高,这种特定驱动下的术前筛查极易导致男性圆锥角膜的临床检出率被动升高,从而在流行病学数据上造成男性偏高的假象[5,73]。性激素是通过何种具体的分子级联信号通路影响角膜基质胶原重塑的,全基因组层面是否存在决定性的性别特异性风险位点[8],这些问题均缺乏结论性证据。

基于现有的性别差异研究,未来的圆锥角膜诊疗应逐步向“性别特异性个体化管理”迈进。例如,针对男性患者需具备更高的预警意识并适时建议早期手术干预,而对于女性患者则需高度关注其妊娠期的疾病突变风险及眼表不适症状的对症处理。

目前圆锥角膜的发病机制尚不明确,其发生受到多种因素如遗传因素、炎症反应、氧化应激及性激素等的共同作用,但相较于圆锥角膜整体发病机制的研究现况,该病在性别差异方面缺少长期的随访调查及充分的遗传学研究。因此与以往相关综述不同[74],本文系统整合了圆锥角膜性别差异的多方面证据,探讨了其潜在影响因素及机制,旨在提高眼科临床医生对圆锥角膜患者性别差异的重视程度,为未来制定更精准、个体化的临床诊疗与干预方案提供参考。

利益冲突声明:本文不存在利益冲突
作者贡献声明:尹晨晨论文选题与修改,初稿撰写,文献检索;袁艺论文修改及审阅;任胜卫选题指导,论文修改及审阅。所有作者阅读并同意最终的文本。

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