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单眼病变引起双侧眼表结构功能改变的研究进展*

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[摘要] 双眼在解剖上看似独立,但在病理生理上相互关联、相互影响。近年来研究显示单眼病变患者的对侧未受累眼存在与患眼相似的眼表结构及功能改变,如角膜神经密度降低、角膜感觉功能减退、角膜细胞减少、泪液分泌减少、泪液因子改变、树突状细胞增多和眼表免疫赦免特性丧失。该文将对单眼病变引起的双侧眼表变化及其发病机制作一综述,以期加深对双眼间关系的认识。

[关键词] 对侧未受累眼;角膜神经;角膜细胞;树突状细胞;泪液;综述

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Advances in bilateral alterations of ocular surface structure and function after monocular lesions*

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[Abstract] Each of the two eyes in humans is encased separately within its bony orbit, and there is no anatomical communication between the two compartments. However they are correlated and influenced by each other in pathophysiology. Recent studies have shown the contralateral unaffected eye of patients with monocular lesions has ocular surface structural and functional changes, which are similar to affected eye, such as the reduction of corneal nerves, the loss of corneal sensation, a diminishment of corneal superficial epithelial cells, corneal endothelial cells and tear secretion, the change of tear cytokines, increased density of dendritic cells and the loss of immune privilege. This article reviews the bilateral changes of ocular surface structure and function and its pathogenesis caused by monocular lesions, hoping for deepening the understanding of binocular relationship.

[Key words] contralateral clinically unaffected eye; corneal nerve; corneal cell; dendritic cell; tear; reviews

单眼病变或手术引起对侧眼损伤的概率极低,眼穿通伤后对侧眼发生交感性眼炎的概率为 0.2%~0.5%,内眼术后仅为 0.01%^[1]。然而,近年大量临床研究和动物实验证明双眼间广泛存在相互作用,单眼损伤及手术患者其对侧未受累眼虽在裂隙灯显微镜下无明显异常,但在角膜神经、角膜感觉功能、角膜细胞、泪液分泌、泪液因子、免疫反应等微观水平已出现与患眼相似的结构功能病变^[2-3],上述微观改变若不及时加以干预可能会继续进展直至出现宏观病变。最近已有学者发现部分单眼病变患者的对侧未受累

眼出现干眼^[4-5]。在现实生活中大部分单眼病变患者的患眼视力较差甚至已经失明,在这种情况下除进行患眼治疗外,重视并保护对侧未受累眼的眼表健康对改善患者的视觉质量、生存质量也十分必要。

1 单眼病变引起双侧角膜神经改变

角膜是人体内神经分布最密集的部位,由三叉神经眼支的终末支——睫状神经支配。角膜神经具有敏锐的感觉功能和营养功能,对维持眼表正常结构功能十分重要^[6]。活体共聚焦显微镜研究显示,与健康对照组比较,单眼单纯疱疹病毒性角膜炎患者双侧角

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膜神经密度降低、角膜神经弯曲度增加、角膜感觉减退,其中对侧未受累眼角膜神经损伤程度轻于患眼。相关分析显示角膜神经主干数量与患病时间、疾病复发次数呈负相关,角膜神经密度降低与角膜感觉减退呈正相关,意味着病毒复发可损伤角膜神经,角膜神经减少可导致角膜感觉功能减退^[7-9]。随后,在单眼带状疱疹性眼病患者身上也发现了类似的双侧角膜神经改变^[10-11]。CRUZAT 等^[12]对单眼细菌性角膜炎、真菌性角膜炎、棘阿米巴性角膜炎患者的双眼进行观察,发现 3 组患侧角膜神经密度、角膜感觉较健康对照组降低,其中棘阿米巴性角膜炎患者的患眼角膜神经损伤较细菌性角膜炎患者、真菌性角膜炎患者重,认为与棘阿米巴原虫的嗜神经特性相关。同患眼比较,3 组患者的对侧未受累眼角膜神经损害较轻,且组间无差异,意味着细菌、真菌、棘阿米巴原虫对对侧未受累眼的角膜神经损害的影响无差异。GIANNACCARE 等^[13]在单眼神经营养性角膜炎患者中发现其双眼角膜神经密度较正常人降低,与重症组比较,轻症组患者的对侧未受累眼角膜神经损伤更为严重,对患眼行角膜神经再生术后,患眼和对侧受累眼均出现角膜神经密度增加,意味着神经再生术能使双眼获益。

除角膜慢性炎症外,角膜急性损伤也会引起双侧角膜神经损害。动物实验证实环形切断一侧眼角膜神经后双眼角膜神经立即减少,这一损害一直持续至术后第 14 天^[14]。最近,GIANNACCARE 等^[15]在单眼白内障手术患者中发现,术后 30 d 双侧角膜神经密度较术前降低、角膜神经形态异常度增加,对侧未手术眼角膜神经受损程度轻于术眼。

上述研究认为患侧/术侧角膜神经损伤与眼表炎症、病原微生物感染、手术机械损伤、治疗时使用的滴眼液药物毒性蓄积作用相关,而对侧未受累眼的角膜神经损伤可能与病原体隐匿性感染相关。疱疹病毒经患眼入侵后,病毒沿轴浆逆行运输至三叉神经节内潜伏,当病毒再次活化时,潜伏的病毒沿神经吻合处向周边游走或自三叉神经节向三叉神经中脑核运动到达对侧眼进而损伤对侧眼角膜神经^[16]。但这一可能性尚不足以完全解释对侧未受累眼的角膜神经损害,因为活体共聚焦显微镜排除了对侧眼真菌、棘阿米巴原虫感染可能。目前,大部分学者认为对侧未受累眼角膜神经损伤与中枢神经系统介导的神经源性调节相关。在非眼科领域里,单侧神经损伤引起对侧区域镜像改变的例子越来越多,对侧区镜像改变提示脊髓或脑回路的参与、外周神经纤维向双侧投射^[17]。当患眼受损时,神经冲动自患眼角膜神经传至大脑中

枢,在中枢神经系统调节下向对侧未受累眼发放神经冲动引起角膜神经损伤。

2 单眼病变引起双侧角膜细胞改变

研究显示单眼单纯疱疹病毒性角膜炎、带状疱疹性眼病患者患眼角膜浅表上皮细胞数量减少、细胞体积增大,上皮细胞形态、数量改变与角膜神经损伤、角膜感觉功能减退明显相关^[18-19]。刘馨甜等^[20]对单眼感染性角膜炎患者(病毒、真菌、细菌)的对侧未受累眼进行观察,发现对侧未受累眼角膜神经密度、角膜上皮细胞密度较对照组降低。MÜLLER 等^[21]发现单眼单纯疱疹病毒性角膜炎患者双侧角膜内皮细胞减少,内皮细胞减少与角膜神经密度降低呈正相关。上述研究表明单眼角膜炎患者双侧角膜细胞损伤与角膜神经减少、角膜神经营养功能减退有关。角膜神经分泌的神经营养介质,如 P 物质、血管活性肠肽、神经生长因子、降钙素基因相关肽等能影响角膜细胞增殖^[22-23],血管活性肠肽能促进角膜内皮创面愈合,并通过抑制干扰素- γ 和肿瘤坏死因子- α 减轻角膜内皮细胞凋亡^[24]。

3 单眼病变引起双侧泪液相关因素改变

3.1 泪液质量改变

干眼的常用诊断指标包括泪膜破裂时间、泪液分泌试验、泪液渗透压。研究发现单眼单纯疱疹病毒性角膜炎患者双眼泪液渗透压增高,泪膜破裂时间、泪液分泌试验降低,泪液损伤程度与患眼角膜感觉减退呈正相关,当患眼角膜知觉严重减退时,双眼即出现干眼表现^[4],类似改变还可见于单侧神经营养性角膜炎患者^[5]。泪液功能单元由眼表、泪腺及二者间的神经构成,任一环节受损均可影响泪液分泌。当患眼角膜神经减少、角膜感觉减退时,双侧泪液分泌反射的传入神经通路发生障碍,引起双眼眨眼频率下降、泪液蒸发过多,从而导致双侧泪液渗透压增高、泪膜稳定性下降。LEE 等^[14]发现单侧角膜环形切开后双眼泪液分泌量减少、泪腺血管活性肠肽水平降低,认为泪液减少与血管活性肠肽水平降低有关。副交感神经释放的神经递质如血管活性肠肽可调节泪腺中水、蛋白质、电解质分泌^[25]。周围三叉神经纤维向脑干核的双侧区延髓尾端投射,当患眼角膜神经减少时,传至大脑中枢的神经冲动减弱,引起双侧传出神经冲动减少,支配泪腺的副交感神经张力减小,刺激泪腺血管活性肠肽分泌减少,引起泪液量降低。

3.2 泪液因子改变

泪液炎性细胞因子与眼病关系密切,能参与疾病发生。YAMAGUCHI 等^[26]对单眼细菌性角膜炎患者的双侧泪液进行检测分析,发现患眼与未受累眼泪

液炎症因子变化水平不一致。与健康对照组比较,患眼泪液表现为白细胞介素(IL)-1 β 、IL-6 和 IL-8 水平升高,且泪液炎症因子变化与患眼角膜树突状细胞密度改变呈正相关,与角膜神经密度变化呈负相关。对侧未受累眼泪液中 IL-10、IL-17a 和趋化因子(CC 基序)配体 2(CCL2)水平升高。研究显示 IL-1 β 能诱导促炎性因子如 IL-6、IL-8 增多,上调巨噬细胞抗菌能力,启动辅助性 T 细胞(Th)1、Th17 适应性免疫反应,增强宿主抗感染能力^[27-28]。IL-6 参与角膜细菌、真菌、病毒感染^[29-30],能引起角膜神经变性,促进巨噬细胞、T 细胞活化,介导适应性免疫^[31]。此外,IL-6 还是角膜伤口愈合的关键因子^[32]。IL-8 可募集并激活白细胞,介导新生血管生成^[33]。对侧未受累眼泪液中 IL-17a、IL-10 水平升高可能源于患眼感染后对侧眼的预防性防御机制。IL-17a 能通过 Th17 细胞反应调节宿主对感染的预防性防御,改善黏膜屏障的功能。在 IL-6 刺激下,中性粒细胞以自分泌方式分泌大量 IL-17a,刺激上皮细胞、成纤维细胞分泌趋化因子、促炎性因子,从而提高活性氧、抗真菌活性^[34]。IL-10 作为一种抗炎因子,能通过巨噬细胞发挥抗炎作用、终止角膜炎性反应^[35]。当细菌性角膜炎患者角膜感染逐渐好转后,患眼泪液中 IL-1 β 、IL-6、IL-17a 降低,对侧未受累眼泪液 IL-17a 降低。YAWATA 等^[36]在单眼角膜基质混浊患者中发现,患眼和其对侧未受累眼泪液中纤维化因子[转化生长因子(TGF)- β 2]、抗纤维化因子(LIF、TGF- β 3)、促炎因子(IL-1b、IL-17、IL-8、干细胞因子、干细胞生长因子-B)较健康对照组明显升高(患眼升高水平大于对侧未受累眼),认为角膜混浊与上述 8 种泪液因子相关。

类似改变还见于眼科手术。YAWATA 等^[36]对单眼角膜内皮移植术患者的双侧泪液进行检测分析,发现术后手术眼和对侧未手术眼泪液中促炎性因子和趋化因子,如 IL-1b、IL-6、IL-8、单核细胞趋化蛋白-1(MCP-1)较术前升高。方蕾等^[37]在单眼白内障手术患者中发现术后 3 周对侧未手术眼房水中 IL-2、IL-6、MCP-1/CCL2、MIP-1d 较第一术眼明显升高,认为白内障手术可引起对侧眼的免疫反应。MCP-1 又称 CCL2,主要由单核细胞和巨噬细胞产生,其为促炎因子,能促进单核细胞、嗜碱性粒细胞、T 细胞增多,诱导细胞分泌 IL-1、IL-6 等炎症因子。在自身免疫性疾病如葡萄膜炎、自身免疫性脑炎、类风湿性关节炎、系统性红斑狼疮中可观察到 MCP-1 升高,抑制 MCP-1 能减轻炎症反应,阻断疾病进展^[38]。对侧未手术眼泪液、房水中 MCP-1 升高可能是手术眼引起的一种交感性炎症反应。

4 单眼病变引起双侧免疫反应改变

树突状细胞是人体内功能最强大的抗原提呈细胞,可识别外来异物,吞噬病原体,刺激 T 淋巴细胞,是先天免疫和获得性免疫系统间的关键环节。研究表明正常角膜组织中含有未成熟树突状细胞,角膜树突状细胞变化反映免疫激活和炎症变化,是评估眼表炎症的重要指标^[39]。近年来,研究发现单眼感染性角膜炎(细菌、真菌、棘阿米巴、病毒)患者双侧角膜树突状细胞密度较正常对照组增多(对侧未手术眼树突状细胞密度小于患眼),且树突状细胞密度与角膜神经密度改变呈负相关,暗示免疫反应与角膜神经相关^[10、12]。POSTOLE 等^[40]在单侧前葡萄膜炎患者的对侧未受累眼中也发现角膜树突状细胞增多。LEE 等^[14]在小鼠模型上证实,环形切断一侧眼角膜神经可刺激双眼角膜树突状细胞成熟化、树突状细胞密度增加。

单眼病变除引起双眼角膜树突状细胞增多外,还可引起对侧未手术眼免疫赦免特性丧失。PAUNIC-KA 等^[41]发现单侧角膜环形切开引起对侧未手术眼角膜免疫赦免特性消失,对侧眼角膜移植 100%失败。这是由于一侧眼角膜神经切断后,对侧未手术眼中与免疫赦免相关的神经肽,如 P 物质、血管活性肠肽急剧增加,P 物质增多使得角膜植片存活所必需的调节性 T 细胞失活。GUZMÁN 等^[42]在角膜烧伤模型中发现单侧角膜损伤引起对侧眼眼表黏膜耐受性丧失,其认为眼表黏膜耐受性破坏与对侧眼结膜中上皮细胞核因子(NF)- κ B 信号增强、成熟树突状细胞增多及对侧淋巴结中的 T 细胞活化相关。

既往人们对交感性眼炎的认识主要局限于宏观表现,事实证明单纯使用裂隙灯显微镜检查会使眼科医生忽略对侧未受累眼的亚临床改变,限制人们对交感性反应的认识。进一步结合实验室检查能帮助人们在微观水平上更好地认识双眼间交感反应,有利于后续有关机制的深入研究。活体共聚焦显微镜作为一种无创成像设备,能在细胞水平上实时动态评估和量化角膜细胞、炎症细胞、角膜神经的改变,对单眼病变或手术患者的双眼定期实施该项检查不仅有利于病变早期发现,还有助于眼科医师评估眼表炎症水平、监测病情变化、制订个性化治疗方案。此外,泪膜破裂时间、泪液分泌试验、眼表染色、泪液渗透压测定、泪液及房水成分分析等检查也能帮助眼科医师评估双眼情况。

目前,人们对对侧未受累眼的微观病理改变认识还有待深入,提早进行干预能否有效阻断病情进展还有待更多、更大样本量的临床研究证明。在今后的临

床诊疗中眼科医生需加强对对侧未受累眼的关注,以期能更好保护患者双眼健康。在科学研究中,需谨慎使用对侧未受累眼作为健康对照,因为这可能导致研究结果差异。

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