

神经营养性角膜炎诊治的研究进展

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摘要

神经营养性角膜炎 (NK) 是由三叉神经支配受损引起的退行性角膜疾病, 可导致自发性角膜上皮破裂、角膜溃疡甚至穿孔。诸多破坏三叉神经支配的疾病均可导致 NK。NK 的早期诊断十分重要, 需要准确收集和审查患者病史并进行完善的眼表检查, 从而确定临床分期。NK 的治疗需基于疾病严重程度进行分期治疗, 除了人工泪液、睑裂缝合术、羊膜移植术等传统的内外科疗法, 目前还有如靶向药物治疗和角膜神经化手术等新兴疗法。本文总结了 NK 的流行病学、临床表现及分类、病因、诊断、鉴别诊断及治疗, 旨在为未来早期诊断和分期治疗 NK 提供参考。

关键词: 神经营养性角膜炎; 角膜炎; 角膜上皮缺损; 三叉神经; 眼部检查

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Research progress in the diagnosis and treatment of neurotrophic keratitis

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Abstract

• Neurotrophic keratitis (NK) is a degenerative corneal disease caused by impairment of trigeminal innervations. It can lead to spontaneous corneal epithelial defects, corneal ulceration and perforation. Early diagnosis of NK is crucial and requires accurate investigation of clinical history and thorough examination of ocular surface to determine clinical stage. Treatment for NK needs to be divided into stages according to disease severity. In addition to conventional treatments including artificial tears, blepharorrhaphy, and amniotic membrane transplantation, there are also emerging treatments such as targeted drug therapy and corneal neurotization. This article summarized the epidemiology, clinical manifestations and classification, etiology, diagnosis, differential diagnosis and treatment of NK, aiming to provide reference for the early diagnosis and treatment of NK in the future.

• **KEYWORDS:** neurotrophic keratitis; keratitis; corneal epithelial defects; trigeminal nerve; eye examination

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0 引言

神经营养性角膜炎 (neurotrophic keratitis, NK), 也被称为“神经麻痹性角膜炎”, 是一种由三叉神经、角膜上皮神经支配受损引起的罕见角膜变性疾病^[1-3]。角膜是人体神经支配最密集的覆盖在眼球前部的透明组织^[4], 角膜感觉神经起源于三叉神经节的眼分支, 在鼻睫状神经及睫状长神经分支中行进, 最终分支成穿透角膜的神经纤维^[5-6]。角膜含有丰富的感觉神经, 能够将各种热、机械和化学刺激转化为眼部干燥、不适或疼痛的意识感知^[7], 从而诱导泪液产生, 刺激眨眼反射^[8], 并且角膜释放多种神经介质, 包括 P 物质 (P substance, SP)、降钙素、神经肽 Y、血管活性肠肽、儿茶酚胺和乙酰胆碱^[9-10]。SP 在炎症后直接从角膜纤维中释放, 与胰岛素样生长因子-1 和表皮生长因子协同作用, 促进上皮增殖和角膜伤口愈合^[11]。NK 是由于角膜神经受损, 导致角膜感觉减退、泪液产生异常, 严重时可能造成持续性角膜上皮缺损 (persistent epithelial defects, PED)、溃疡和基质穿孔, 危及视力^[12]。

1 流行病学

NK 被欧洲药品管理局 (EMA) 孤儿药品委员会 (COMP) 归类为孤儿疾病 (ORPHA137596), 这也印证了 NK 的罕见。根据目前已有流行病学调查, 估计 NK 的患病率低至 1.6/10000^[13]。Saad 等^[14] 统计了 2009-2017 年在三级转诊中心柴尔德基金会医院接受检查的患

者,在筛选的约30万名患者中,NK发病率为0.11%,这是关于NK流行病学、病因、治疗和结果的最大观察性研究,该研究显示,NK发病率比既往文献中报道的更高,NK部分病例延迟诊断表明多数眼科医生对这种疾病的认识仍需提高。

2 病因

任何损害三叉神经支配的情况均可能导致NK^[15],如疱疹病毒感染、眼表疾病、眼部手术、外科手术、全身性疾病、遗传性疾病等。

2.1 疱疹病毒感染 单纯疱疹病毒(herpes simplex virus, HSV)和带状疱疹病毒(herpes zoster virus, HZV)感染是NK最常见的病因,约占NK病例的27%~32%^[16]。

2.2 眼表疾病 各种眼表疾病,如慢性睑缘炎、角膜化学烧伤、睑内翻、角膜营养不良等均可导致NK^[17]。

2.3 眼部手术 角膜手术(角膜切口、角膜移植术、玻璃体切除术、屈光手术)等医源性原因可导致NK。

2.4 外科手术 由于肿瘤、动脉瘤、面部创伤、三叉神经痛等进行外科手术导致三叉神经损伤也会出现NK^[18]。

2.5 全身性疾病 一些全身性疾病,如维生素A缺乏症、多发性硬化症、糖尿病性神经病、麻风病也可导致三叉神经支配受损^[16]。神经病变是糖尿病最常见的并发症之一,糖尿病患者的角膜神经评估表明,角膜敏感性降低与基底神经密度降低有关,神经纤维束异常弯曲,另有研究发现角膜敏感性降低与躯体多发性神经病程度具有相关性^[19-20]。

2.6 遗传性疾病 一些遗传性疾病,如Riley Day综合征(家族自主神经功能障碍)、莫比乌斯角膜感觉减退、Goldenhar-Gorlin综合征和先天性角膜麻醉可引起神经受损,导致NK,但该情况较为罕见^[21]。

3 临床表现及分类

NK患者很少主诉眼部症状,临床表现与症状之间存在差异,其最常见的首发症状包括眼红、畏光、干涩、视力下降和眼疲劳^[22],根据“Mackie分类”^[23],NK的临床表现基于角膜受累严重程度可划分为轻(1期)、中(2期)、重(3期)三个阶段。1期NK是疾病最常见的表现,其特征是存在角膜上皮增生和不规则性,导致角膜上皮混浊,但没有明显的上皮缺损,检查可见角膜上皮不规则性,表现为点状上皮糜烂、Gaule斑点和泪膜破裂时间减少。2期NK的特征是角膜上皮缺损而不累及间质,通常存在PED,主要位于角膜上部中央附近区域,呈椭圆形或圆形,且由于愈合受损而具有光滑、卷曲及松散的边缘,被称为“卷边征”。3期NK的定义是角膜上皮缺损加上基质受累,病变范围从轻度基质变薄到角膜穿孔,部分患者甚至在没有明显眼部症状的情况下发生3期NK^[24]。

4 诊断

由于引起NK的病因众多,临床医生应准确收集和审查患者的病史并进行仔细的眼表检查。全面审查病史有助于避免NK的延迟诊断,前文所述各种眼表疾病、外科手术、遗传因素等导致NK的病因都应仔细询问。眼表检查十分重要,裂隙灯检查是观察角膜损伤严重程度、判断NK症状及分类的基础,角膜缺损范围从点状角膜病变到基质融化和角膜穿孔^[24],用荧光素或丽丝胺绿进行染色有助于评估角膜和结膜上皮的完整性并识别黏液丝。角

膜敏感性降低或消失是NK的诊断标志^[25],评估角膜敏感性对于确诊NK和评估角膜神经损伤的严重程度至关重要。角膜敏感性可以通过用棉线触摸中央和周围角膜或使用角膜感觉计定量测量^[25]。Cochet-Bonnet感觉计^[26]采用长度可调的尼龙单丝接触角膜并记录患者的反应,可以测试角膜的每个象限,随着灯丝长度的减少,传递的压力随之增加。Belmonte非接触式感觉仪基于不同温度、压力和一氧化碳浓度下气体脉冲引导至角膜后产生的角膜刺激,与Cochet-Bonnet感觉计相比,这种非接触式仪器除了机械刺激外还可产生化学刺激^[27]。体内共聚焦显微镜也被引入常规临床评估,以研究角膜的细胞结构,包括基底神经和基底下神经,并提供与离体组织化学方法相当的图像,不同类型的体内共聚焦显微镜已被用于评估NK患者的角膜神经形态和变化^[28]。

5 鉴别诊断

点状角膜病变和泪膜异常是NK 1期的特征^[23],在其他眼部疾病(如干眼、暴露性角膜炎、局部药物毒性、角膜缘干细胞缺乏症)中也可出现。NK患者出现烧灼感、异物感、畏光和干眼等症状可能会使临床医生误诊为其他眼表疾病,但NK的诊断标志是角膜敏感性降低,Cochet-Bonnet感觉计、Belmonte非接触式感觉仪检查有助于明确诊断。感染性、毒性或免疫性角膜溃疡也可表现为严重的眼部炎症、基质浸润等,故临床病史、体征和症状及细菌、真菌和病毒微生物检测结果对诊断NK十分必要,临床医生应停止所有局部治疗以排除医源性角膜溃疡,并应考虑评估患者是否存在其他全身免疫性疾病。糖尿病患者由于代谢异常,引起角膜神经营养低下,角膜周围血管网的血液流通不畅,导致糖尿病性角膜病变,患者既往糖尿病病史、症状和体征有助于鉴别诊断。

6 治疗

NK应早期诊断并基于疾病的严重程度分期治疗^[25]。第1阶段治疗旨在改善角膜上皮质量和透明度,避免角膜上皮破裂。应停用所有外用药物,因为它们对眼表上皮有不利影响。目前尚无针对NK的药物,不含防腐剂的人工泪液可能有助于改善疾病严重程度、润滑眼表^[29]。

第2阶段治疗旨在促进角膜上皮缺损的愈合,并防止进展为角膜溃疡^[28],包括治疗性角膜绷带镜^[29]、局部自体或同种异体血清及抗炎药物治疗。Cenegermin是一种含有20 μg/mL重组人神经生长因子(recombinant human nerve growth factor, rhNGF)的眼用溶液,是第一种被批准用于治疗NK的药物^[30]。Cheung等^[31]发现在配戴绷带隐形眼镜联合使用Cenegermin滴眼液治疗PED,67%的患者PED完全愈合,33%的患者症状改善。自体血清滴眼液自1999年以来经常用于治疗角膜上皮缺损^[32-34],与传统的泪液替代品相比,自体血清中乳铁蛋白、谷胱甘肽和维生素C的浓度较低,但白蛋白、纤维蛋白、免疫球蛋白(IgM和gG)、溶菌酶和生长因子[如神经生长因子(nerve growth factor, NGF)、血小板衍生生长因子、转化生长因子β1(transforming growth factor β1, TGF-β1)和表皮生长因子]浓度较高,这些物质可促进角膜上皮细胞增殖、迁移和分化,对角膜稳态和伤口愈合至关重要^[35],有助于维持眼表的稳定性^[36-37]。Shtein等^[38]检索并分析4项采用自体血清治疗PED的研究,所有研究均显示症状有所改善,

其中3项研究显示改善率超过90%。Guadilla等^[39]研究对处于Mackie分类不同阶段的NK患者19例22眼进行纵向、观察性和描述性研究,结果显示使用20%自体血清是治疗1、2期NK的有效方法,但不足以治疗3期NK。

第3阶段手术治疗通常仅限于对药物治疗无反应和/或出现相关并发症的角膜溃疡,手术方式包括羊膜移植术(amniotic membrane transplantation, AMT)、睑裂缝合术及结膜覆盖术^[28]。羊膜(amniotic membrane, AM)具有促进角膜上皮细胞迁移,加强基底细胞黏附和促进角膜上皮细胞分化的能力,其调节基质瘢痕形成的能力及抗炎活性促使AM被广泛用于眼表手术^[40-41]。治疗难治性NK时应考虑AMT。AMT相对容易进行,可有效促进角膜上皮愈合,减少血管形成,减少眼表炎症^[42-43]。Turkoglu等^[44]将AMT与自体血清进行比较,发现两者在治疗NK引起的角膜溃疡方面同样有效。Schuerch等^[45]回顾性分析评估2012-2017年接受AMT治疗的难治性角膜溃疡患者,发现神经营养性角膜溃疡的愈合率最高(93%),表明AMT是一种有价值的治疗选择,可在常规治疗效果不佳的情况下实现角膜上皮伤口愈合。既往睑裂缝合术曾被认为是NK治疗的金标准,Cosar等^[46]研究中超过90%的病例角膜上皮在睑裂缝合术后18d内愈合,其中多数患者角膜上皮缺损由NK引起。结膜瓣的使用由Gundersen^[47]于1958年首次提出,能够恢复眼表完整性,但并不能恢复视觉功能,生长因子和营养物质可通过结膜血管输送到角膜,并去除促炎蛋白酶^[48]。360°切开后,从上球结膜取出带蒂的结膜瓣,根据角膜缺损的大小和定位,将其固定在缺损处^[49]。结膜覆盖术后角膜上皮细胞快速上皮化,约4-6wk内从周围完整的角膜上皮细胞中置换^[50]。睑裂缝合术和结膜覆盖术均是促进角膜愈合的有效外科手术,但二者缺点也很明显,影响外观,并且阻碍患者的视觉功能^[51]。

7 新兴疗法

目前,尽管内科和外科治疗方案在角膜伤口愈合和预防NK进展方面取得了部分成功,但仍需要新的治疗药物以获得更好的临床结果。一些新型治疗方案通常是通过靶向参与角膜伤口愈合或NK发病机制的细胞或分子来开发的。角膜伤口愈合是一个复杂的过程,涉及细胞死亡、迁移、增殖、分化和细胞外基质重塑^[52]。在伤口愈合的所有阶段中发挥积极作用的都可以被视为新的治疗剂。角膜上皮愈合取决于角膜缘上皮干细胞和基底膜的重塑^[53]。生长因子和细胞因子在角膜伤口愈合过程中也起主要作用,包括生长、增殖和黏附等^[54]。因此,大量靶向药物可能会加速角膜伤口愈合,包括表皮生长因子、TGF- β 1、胸腺素 β 4(thymosin β 4, T β 4)^[55]、血小板衍生生长因子和NGF^[56-57]。

7.1 新型治疗剂

7.1.1 富血小板血浆 富血小板血浆(platelet-rich plasma, PRP)是一种不含防腐剂的自体血液制品,富含蛋白质和生长因子,促进细胞分化、增殖和迁移,从而刺激组织的愈合和再生^[58]。Wróbel-Dudzińska等^[59]选取NK患者25例,每天给予5次自体PRP滴剂,并在夜间给予不含防腐剂的人工泪液和维生素A软膏,治疗时间最长为3mo,治疗后20例患者(80%)角膜溃疡完全愈合,4例患者

(16%)临床症状明显改善,另有1例患者由于病情较为复杂,最后进行了AMT。

7.1.2 T β 4 T β 4是一种细胞内蛋白,在不同的细胞过程中具有多种功能,已被证明可以加速细胞迁移和再上皮化,减少促炎细胞因子的释放,抑制核因子- κ B^[60]。一项开放研究观察了4例NK患者的治疗情况,纳入患者均显示角膜上皮缺损范围显著减少,表明T β 4治疗NK具有很大作用^[61]。

7.1.3 再生剂 再生剂(regenerating agents, RGTA)可用于中重度NK的治疗。RGTA是一种基质剂,含有模拟硫酸乙酰肝素的大型聚合物,可产生诱导细胞迁移和黏附并促进角膜上皮愈合的微环境^[62-63]。Pereira等^[64]报告了1例73岁神经营养性角膜溃疡患者,接受RGTA治疗后角膜完全愈合、视觉功能显著恢复。

7.2 新兴外科手术疗法 新兴的一些外科手术疗法也应用于临床。角膜神经化是一种将健康神经从其他区域转移到无敏角膜的手术,已成为NK患者的优先手术治疗选择^[65-66],可通过两种不同的方式进行,即基于眶上和/或滑车上神经的转位(直接神经化)^[67]或腓肠神经移植(间接神经化)^[68]。Rowe等^[69]报告了1例17岁因Ramos-Arroyo综合征继发NK的患者,接受双侧角膜神经化术,该手术通过腓肠神经自体移植物延伸的大耳神经转移进行,能够为患者提供更快、更有效、更安全的手术方案。Rusňák等^[70]报告了1例既往有神经外科手术史的男性患者,右眼球挫伤后右眼视力下降,出现PED,接受自体腓肠神经移植术后5mo,右眼角膜的敏感性开始恢复。角膜神经化术后广泛性角膜上皮缺损愈合,证明使用眶上神经和自体感觉神经移植是治疗重症NK的新的解决方案。

8 小结与展望

NK是一种较为罕见的退行性疾病,目前多数眼科医生对其认识不足,临床误诊时有发生,鉴于此,提高眼科医生对该病的诊治水平十分必要。早期诊断、分期治疗有助于维持角膜完整性和预防疾病进展。本文总结了多种药物和手术治疗方式及一些较为新颖的突破性疗法,目前大多治疗方法集中在预防疾病进展上,但部分新兴药物和外科手术可针对其致病原因,作用于角膜神经的直接功能和结构。未来仍需要进一步的研究是否有更准确的诊断方法及更有效的治疗方案继续扩展关于NK疾病预防、识别和治疗方面的知识。

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