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• 临床研究 •

角膜激光共聚焦显微镜在单眼感染性角膜炎疾病诊断中的应用*

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摘要 目的:探讨角膜激光共聚焦显微镜在单眼感染性角膜炎疾病诊断中的应用价值。**方法:**回顾性研究 2020 年 6 月到 2021 年 6 月选择在本院诊治的单眼感染性角膜炎疾病患者 62 例,所有患者都给予角膜激光共聚焦显微镜检查,记录影像学特征并判断诊断价值(以病原学诊断为金标准)。**结果:**真菌性角膜炎在角膜激光共聚焦显微镜下的病变区纵横交错的高反射的真菌菌丝或高反光细长颗粒状的孢子,细菌性角膜炎的病变处会聚集活化的树突状细胞及大量的炎症细胞,病毒性角膜炎的基底膜下神经纤维密度、神经主干的分支数减少,棘阿米巴性角膜炎的包囊表现为圆形高反光厚壁结构。角膜激光共聚焦显微镜判断为病毒性角膜炎 17 例,诊断病毒性角膜炎的敏感性与特异性为 94.4% 和 100.0%;角膜激光共聚焦显微镜判断为棘阿米巴性角膜炎 4 例,诊断棘阿米巴性角膜炎的敏感性与特异性为 94.4% 和 100.0%;角膜激光共聚焦显微镜判断为细菌性角膜炎 21 例,诊断细菌性角膜炎的敏感性与特异性为 95.5% 和 97.5%;角膜激光共聚焦显微镜判断为真菌性角膜炎 20 例,诊断真菌性角膜炎的敏感性与特异性为 94.4% 和 93.2%。ROC 曲线分析显示角膜激光共聚焦显微镜诊断细菌性角膜炎、真菌性角膜炎、病毒性角膜炎、棘阿米巴性角膜炎的曲线下面积分别为 0.525、0.579、0.777、0.731。**结论:**角膜激光共聚焦显微镜在单眼感染性角膜炎疾病诊断中的应用能较好的区分细菌性角膜炎、真菌性角膜炎、病毒性角膜炎、棘阿米巴性角膜炎,具有良好的诊断敏感性与特异性。

关键词:角膜激光共聚焦显微镜;细菌性角膜炎;真菌性角膜炎;病毒性角膜炎;棘阿米巴性角膜炎

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Application of Corneal Laser Confocal Microscope in the Diagnosis of Monocular Infectious Keratitis*

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ABSTRACT Objective: To explore the application values of corneal laser confocal microscope in the diagnosis of monocular infectious keratitis. **Methods:** From June 2020 to June 2021, Retrospective study of 62 cases of patients with monocular infectious keratitis disease, all patients were given corneal laser confocal microscopy, and were to record the imaging characteristics and judged the diagnostic value (Based on pathogenic diagnosis as the gold standard). **Results:** In fungal keratitis, there were highly reflective fungal hyphae or highly reflective slender granular spores criss-crossed in the lesion area under corneal laser confocal microscope, and activated dendritic cells gather in the lesion of bacterial keratitis. And there were large number of inflammatory cells, the density of nerve fibers under the basement membrane and the number of branches of the nerve trunk of viral keratitis are reduced, and the cysts of acanthamoebic keratitis show round, high-reflective, thick-walled structure. The corneal laser confocal microscope judged 17 cases of viral keratitis, the sensitivity and specificity of diagnosing viral keratitis were 94.4% and 100.0%; corneal laser confocal microscope judged 4 cases of acanthamoebic keratitis, diagnosis The sensitivity and specificity of acanthamoebic keratitis were 94.4% and 100.0%; 21 cases of bacterial keratitis were judged by corneal laser confocal microscope, and the sensitivity and specificity for the diagnosis of bacterial keratitis were 95.5% and 97.5%; 20 cases of fungal keratitis were judged by corneal laser confocal microscope, and the sensitivity and specificity of diagnosing fungal keratitis were 94.4% and 93.2%. ROC curve analysis showed that the area under the curve for the diagnosis of bacterial keratitis, fungal keratitis, viral keratitis, and Acanthamoebic keratitis by corneal laser confocal microscope were 0.525, 0.579, 0.777, 0.731, respectively. **Conclusion:** The application of corneal laser confocal microscope in the diagnosis of monocular infectious keratitis can distinguish bacterial keratitis, fungal keratitis, viral keratitis, and acanthamoebic keratitis, and have good diagnosis. Sensitivity and specificity.

Key words: Corneal laser confocal microscope; Bacterial keratitis; Fungal keratitis; Viral keratitis; Acanthamoebic keratitis

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前言

角膜炎为临床上的常见眼科疾病,也是造成患者失明的重要病因。感染性角膜炎为角膜炎的主要类型,病原体包括细菌、病毒、真菌,该病可反复发作,多单眼发病,严重威胁视功能^[1,2]。感染性角膜炎多发生于小儿,早期发病时的临床症状不明显,随着病情的进展可出现急性滤泡性结膜炎、树枝状角膜炎、点状角膜炎、疱疹性水疱等,具有一定的自限性^[3,4]。但当患者进展至眼内炎与角膜穿孔时,预后较差,需及时进行眼球摘除手术,为此加强早期诊断具有重要价值^[5]。多种病原体可引起角膜感染,只有在早期进行快速诊断,才可进行对症治疗,改善患者预后,降低致盲率^[6,7]。临床上诊断单眼感染性角膜炎的方法包括临床症状、角膜刮片培养等,但存在诊断时间长、敏感性低等不足,且受取材限制较大^[8,9]。随着医学技术的发展,角膜激光共聚焦显微镜得到了广泛应用,其为一种新型活体生物检查技术,可通过动态观察角膜组织细胞形态,具有高检出率、及时高效、无创等优点。特别是角膜激光共聚焦显微镜可对活体角膜进行非侵入的检查,被不同病原体感染的角膜显现不同的特征^[10,11]。本文具体探讨了角膜激光共聚焦显微镜在单眼感染性角膜炎

疾病诊断中的应用,以促进感染性角膜炎的早期检出。

1 资料与方法

1.1 研究对象

回顾性研究 2020 年 6 月到 2021 年 6 月选择在本院诊治的单眼感染性角膜炎疾病患者 62 例。

纳入标准:临床确诊为单一类型病原体感染的角膜炎患者;本院伦理委员会批准了此次研究;符合 4 种角膜炎之一的诊断标准;患者均存在不同程度的眼部不适或疼痛、视力下降、畏光等症状。

排除标准:妊娠与哺乳期妇女;既往和现有眼部疾病史、外伤史等患者;≥2 种病原体混合感染者;临床诊断感染病原体不确定者;合并恶性肿瘤的患者;临床资料缺乏者。

以角膜溃疡标本实验室培养结果为金标准,62 例患者中细菌性角膜炎 22 例、真菌性角膜炎 18 例、病毒性角膜炎 18 例、棘阿米巴性角膜炎 4 例。不同类型患者的性别、年龄、病程、体重指数、患眼位置、患眼最佳矫正视力、患眼眼压等对比差异无统计学意义($P>0.05$)。见表 1。

表 1 不同类型单眼感染性角膜炎患者的一般资料对比

Table 1 Comparison of general data of patients with different types of monocular infectious keratitis

Groups	n	Gender (male/female)	Age (years)	Course of disease (month)	Body mass index (kg/m ²)	Location of affected eye (left eye/right eye)	Best corrected vision of the affected eye	Intraocular pressure in the affected eye (mmHg)
Bacterial keratitis	22	11/11	34.69± 3.22	1.98± 0.21	22.17± 1.46	13/9	4.45± 0.15	15.31± 1.58
Fungal keratitis	18	9/9	34.16± 4.05	1.92± 0.18	22.09± 2.17	10/8	4.42± 0.22	15.29± 1.22
Viral keratitis	18	10/8	34.98± 2.75	1.99± 0.24	22.18± 1.46	10/8	4.41± 0.18	15.28± 1.63
Acanthamoeba keratitis	4	2/2	34.22± 3.19	1.94± 0.33	22.19± 2.75	2/2	4.42± 0.18	15.33± 1.11

1.2 角膜激光共聚焦显微镜检查

所有患者都给予角膜激光共聚焦显微镜检查,采用 0.4% 盐酸奥布卡因滴眼液滴眼 3 次。使用德国海德堡公司的激光共聚焦显微镜(激光波长 670 nm,放大倍数 800,观察视野 380 μm× 380 μm,分辨率为 1 μm),将患者眼睑打开,其下颌部置于检查架上,保持前额紧贴检查架。保持患者静止,并注视前方凝视光点。前移物镜使物镜通过凝胶接触角膜。于角膜表面移动物镜,对角膜溃疡病灶区及其周围区域行全面扫描,可获得角膜各层扫描图像,选取清晰图像进行保存与分析。

1.3 病原学检查

所有患者给予眼部取样病原学检查,严格无菌操作,表面麻醉角膜,刮取坏死角膜组织,送病原学实验室检测病原体阳性情况,以病原学诊断结果作为诊断的金标准。同时所有患者给予裂隙灯显微镜检查,记录影像学特征。

最终临床确诊由 2 名具有 5 年以上角膜病诊治经验的副主任医师共同诊断,意见不一致时邀请眼科主任医师进行最终判定。

1.4 统计学分析

选择 SPSS20.00 软件分析,计量数据以($\bar{x} \pm s$)表示,计数

数据采用(n/%)表示,两两对比为卡方 χ^2 检验与 t 检验等,多组间对比为方差分析等, $P<0.05$ 为差异有统计学意义,检验水准为 $\alpha=0.05$ 。

2 结果

2.1 裂隙灯显微镜下特征对比

(1)真菌性角膜炎 可见菌丝苔被,存在浸润病灶或小脓包,多位于角膜的中央及中央偏下区域,外观干燥,无光泽,病变区域灰白色隆起。

(2)细菌性角膜炎 浸润区上皮水肿、基质渗出,角膜中央区的圆形灰白色与黄色浸润灶,边界较清楚,伴有脓性与黄色分泌物。

(3)病毒性角膜炎 出现树枝状或地图状浸润,伴随有前房积脓,角膜中央区出现部位黄色脓包,角膜比较模糊,部分可见角膜云翳或斑翳。

(4)棘阿米巴性角膜炎 角膜前基质层出现斑状、半环状或环状浸润,周围基质水肿,存在大量血管细微结构,可见白色略隆起于角膜表面的小圆形浸润灶。

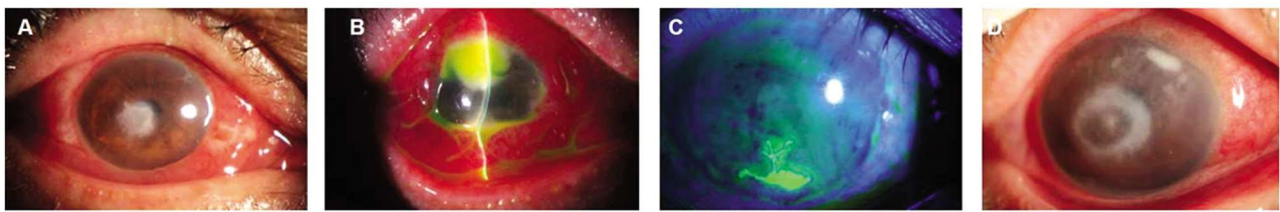


图 1 裂隙灯显微镜下特征

Fig.1 Characteristics under slit-lamp microscope

注: A 图为真菌性角膜炎; B 图为细菌性角膜炎; C 图为病毒性角膜炎; D 图为棘阿米巴性角膜炎

Note: (A) Fungal keratitis; (B) Bacterial keratitis; (C) Viral keratitis; (D) Acanthamoeba keratitis.

2.2 角膜激光共聚焦显微镜下特征对比

(1) 真菌性角膜炎 病变区纵横交错的高反射的真菌菌丝或高反光细长颗粒状的孢子, 基质纤维增生活跃, 伴炎症细胞的浸润, 菌丝相对杂乱, 并可见分隔和分支。

(2) 细菌性角膜炎 病变处会聚集大量活化的炎症细胞与树突状细胞, 伴随有边缘角膜组织水肿, 病灶区组织结构不清。

(3) 病毒性角膜炎 基底膜下可见大量活化的树突状细胞, 神经纤维密度、神经主干的分支数有所减少, 神经纤维直径变小。

(4) 棘阿米巴性角膜炎 包囊表现为 20-25 μm 大小的圆形高反光厚壁结构, 数量不一, 杂乱无章, 部分存在基质内空腔。

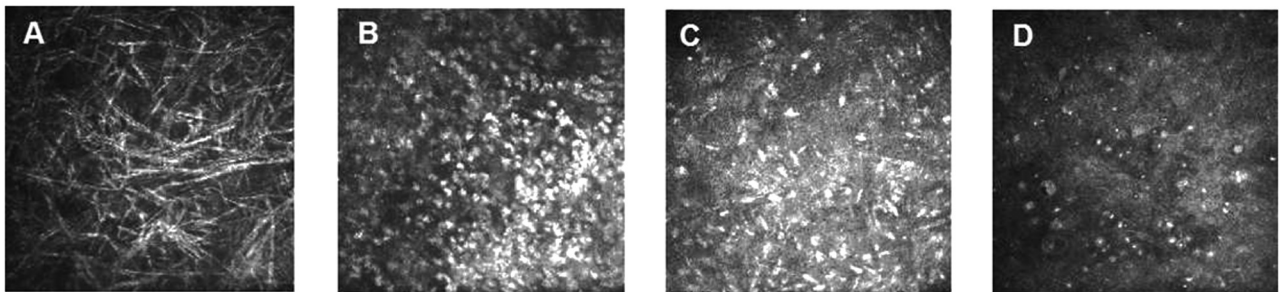


图 2 角膜激光共聚焦显微镜下特征

Fig.2 Features of cornea under confocal laser microscopy

注: A 图为真菌性角膜炎; B 图为细菌性角膜炎; C 图为病毒性角膜炎; D 图为棘阿米巴性角膜炎。

(A) Fungal keratitis; (B) Bacterial keratitis; (C) Viral keratitis; (D) Acanthamoeba keratitis.

2.3 细菌性角膜炎诊断效果

在 62 例患者中, 角膜激光共聚焦显微镜判断为细菌性角

膜炎 21 例, 诊断细菌性角膜炎的敏感性与特异性为 95.5 % (21/22) 和 97.5 % (39/40)。见表 2。

表 2 角膜激光共聚焦显微镜在单眼细菌性角膜炎诊断的敏感性与特异性 (n=64)

Table 2 Sensitivity and specificity of laser confocal microscopy in the diagnosis of monocular bacterial keratitis (n=64)

Clinical diagnosis	Confocal laser microscopy of cornea		Summation
	Positive	Negative	
Positive	21	1	22
Negative	0	39	40
Summation	21	41	62

2.4 真菌性角膜炎诊断效果

在 62 例患者中, 角膜激光共聚焦显微镜判断为真菌性角

膜炎 20 例, 诊断真菌性角膜炎的敏感性与特异性为 94.4 % (17/18) 和 93.2 % (41/44)。见表 3。

表 3 角膜激光共聚焦显微镜在单眼真菌性角膜炎诊断的敏感性与特异性 (n=64)

Table 3 Sensitivity and specificity of laser confocal microscopy in the diagnosis of monocular fungal keratitis (n=64)

Clinical diagnosis	Confocal laser microscopy of cornea		Summation
	Positive	Negative	
Positive	17	1	18
Negative	3	41	44
Summation	20	42	62

2.5 病毒性角膜炎诊断效果

在 62 例患者中,角膜激光共聚焦显微镜判断为病毒性角

膜炎 17 例,诊断病毒性角膜炎的敏感性与特异性为 94.4 % (17/18)和 100.0 % (44/44)。见表 3。

表 4 角膜激光共聚焦显微镜在单眼病毒性角膜炎诊断的敏感性与特异性(n=64)

Table 4 Sensitivity and specificity of laser confocal microscopy in the diagnosis of monocular viral keratitis (n=64)

Clinical diagnosis	Confocal laser microscopy of cornea		Summation
	Positive	Negative	
Positive	17	1	18
Negative	0	44	44
Summation	14	45	62

2.6 棘阿米巴性角膜炎

在 62 例患者中,角膜激光共聚焦显微镜判断为棘阿米巴

性角膜炎 4 例,诊断棘阿米巴性角膜炎的敏感性与特异性为 94.4 % (4/4)和 100.0 % (58/58)。见表 4。

表 5 角膜激光共聚焦显微镜在单眼棘阿米巴性角膜炎诊断的敏感性与特异性(n=64)

Table 5 Sensitivity and specificity of laser confocal microscopy in the diagnosis of acanthamoeba keratitis (n=64)

Clinical diagnosis	Confocal laser microscopy of cornea		Summation
	Positive	Negative	
Positive	4	0	4
Negative	0	58	58
Summation	4	58	62

2.7 诊断价值分析

ROC 曲线分析显示角膜激光共聚焦显微镜诊断细菌性角

膜炎、真菌性角膜炎、病毒性角膜炎、棘阿米巴性角膜炎的曲线下面积分别为 0.525、0.579、0.777、0.731。见图 1。

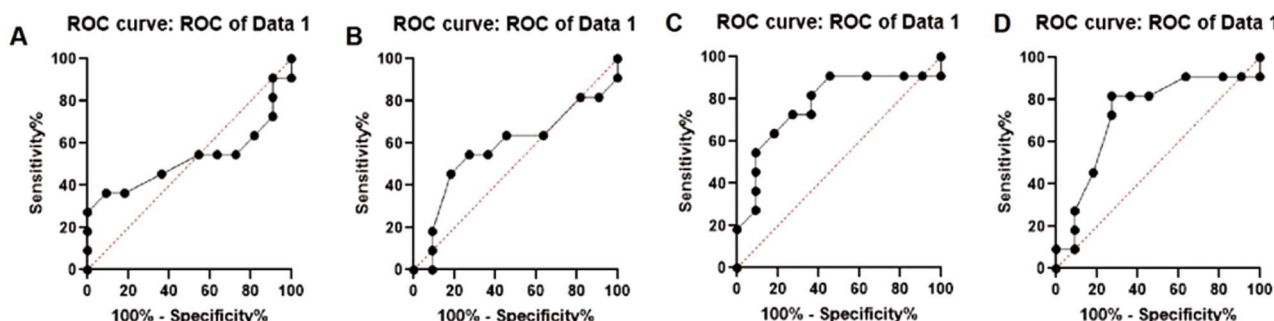


图 3 ROC 曲线分析

Fig.3 ROC curve analysis

注:A 图为真菌性角膜炎;B 图为细菌性角膜炎;C 图为病毒性角膜炎;D 图为棘阿米巴性角膜炎。

(A) Fungal keratitis; (B) Bacterial keratitis; (C) Viral keratitis; (D) Acanthamoeba keratitis.

3 讨论

感染性角膜炎是最常见的致盲性角膜疾病之一,许多患者常因误诊或得不到及时有效的治疗而导致失明^[12,13]。感染性角膜炎若长期不进行治疗,多数患者可出现角膜穿孔^[14,15]。角膜感染的主要病原体为真菌、细菌、病毒。近年来,棘阿米巴角膜炎也在逐渐上升^[16]。

感染性角膜炎的早期诊断至关重要,可有效改善患者预后。感染性角膜炎的传统辅助检查是病原学的实验室检查,也为诊断的金标准,但取样部位为角膜,诊断方法受取材限制较大,很难作为普查方法^[17]。裂隙灯检查的敏感性较多,但存在一

定的主观性。角膜激光共聚焦显微镜作为一种非侵入性图像采集设备,可在细胞水平分析眼表结构,在无创前提下获得角膜缘及结膜、角膜的高清晰图像,具有微创、直观、重复性佳等特点^[18-20]。本研究显示:真菌性角膜炎在角膜激光共聚焦显微镜下的病变区纵横交错的高反射的真菌菌丝或高反光细长颗粒状的孢子,伴炎症细胞的浸润,基质纤维增生活跃,菌丝见分隔和分支。细菌性角膜炎的病变处会有大量树突状细胞及炎症细胞聚集活化,导致无法辨别病灶区组织结构。病毒性角膜炎的基底膜下将会减少神经纤维密度以及神经主干分支数,缩短神经纤维直径。棘阿米巴性角膜炎的包囊表现为 20-25 μm 大小的圆形高反光厚壁结构,存在基质内空腔。这一结果与 Borecka A

等人^[21]以及 Fleiszig S M J^[22]等的研究具有一致性,即真菌性角膜炎发生病变时,将会明显破坏角膜各层形态结构,严重者将减低溃疡底部组织透过度,深层基质及内皮不能窥入。细菌性角膜炎病变处会聚集大量活化的炎症细胞与树突状细胞,伴有边缘角膜组织水肿。病毒性角膜炎基底膜下可见大量活化的树突状细胞,神经纤维密度、神经主干的分支数有所减少。棘阿米巴角膜炎包囊表现为 20-25 μm 大小的圆形高反光厚壁结构,数量不一,杂乱无章^[23]。

感染性角膜炎患者具有起病缓慢、病程较长的特点,角膜溃疡在发病数天内出现^[24,25]。本研究显示:在 62 例患者中,诊断细菌性角膜炎的敏感性与特异性为 95.5 % (21/22) 和 97.5 % (39/40); 诊断真菌性角膜炎的敏感性与特异性为 94.4 % (17/18) 和 93.2 % (41/44); 诊断病毒性角膜炎的敏感性与特异性为 94.4 % (17/18) 和 100.0 % (44/44); 诊断棘阿米巴性角膜炎的敏感性与特异性为 94.4 % (4/4) 和 100.0 % (58/58)。这一结果与 Moshirfar M^[26]以及 Nominato L F^[27]等团队的研究具有一致性,从机制上分析,角膜激光共聚焦显微镜为一种活体生物检查技术,它的工作原理是使用共扼焦点技术,具有高分辨率和高图像对比度的特点,可利用激光扫描对角膜组织进行三维空间显示,能够在细胞水平对活体角膜动态观察,从而提高诊断效果。特别是该方法可在数十秒到几分钟内对角膜进行全面的检查,对活体角膜进行非接触性检查,实时观察角膜组织细胞变化,几乎角膜上任何细小的变化都可检测到,从而对各种类型病原体的感染性角膜炎均具有很好的诊断效果^[28,29]。

真菌性角膜炎的主要病原菌为镰刀菌和曲霉菌。研究认为局部外伤、广谱抗生素的使用等均是真菌性角膜炎发病的危险因素^[30]。细菌、病毒与棘阿米巴性角膜炎入侵破坏角膜后,在角膜组织内生长繁殖,并通过产生真菌可溶性抗原、真菌毒素等促进菌丝在角膜内扩散,进而造成导致角膜炎症反应,严重情况下可导致角膜穿孔等^[31]。本研究 ROC 曲线分析显示:角膜激光共聚焦显微镜诊断细菌性角膜炎、真菌性角膜炎、病毒性角膜炎、棘阿米巴性角膜炎的曲线下面积分别为 0.525、0.579、0.777、0.731。与 Pandey M^[32]以及 Rodriguez-Garcia A^[33]的结果具有相似性,分析其原因可知,角膜激光共聚焦显微镜在临床上存在一定的漏诊、误诊情况。角膜激光共聚焦显微镜直接观察到细菌具有一定的困难性,更不可能观察到病毒,两者有易混淆的地方,但能观察细菌和单疱病毒引起的角膜结构变化,为此在鉴别诊断上存在一定的不足^[34]。本研究也存在一定的不足,未与其他检查方法进行对比,纳入患者数量较少,未纳入眼部健康者,将在后续研究中进行探讨。

总之,角膜激光共聚焦显微镜应用于单眼感染性角膜炎疾病诊断中能较好的区分细菌性角膜炎、真菌性角膜炎、病毒性角膜炎、棘阿米巴性角膜炎,具有良好的诊断敏感性与特异性。

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