

影响湿性年龄相关性黄斑变性治疗应答不良的相关因素研究进展

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摘要

湿性年龄相关性黄斑变性 (wARMD) 是引起中老年人视力不可逆性下降的主要原因之一。目前, 临床一线使用的抗血管内皮生长因子 (VEGF) 药物在治疗 wARMD 上效果显著。然而在实际临床应用中, 对抗 VEGF 药物治疗的预后表现存在显著的个体差异, 部分患者对治疗表现出应答不良现象, 究其原因可能与黄斑区视网膜各层结构的形态学差异、遗传基因学、全身情况等因素相关。提前根据患者不同的临床表现判断其预后, 将有助于制定更加合理的个体化治疗方案, 以减少过度治疗, 从而降低对视网膜损伤的风险。近年来关于治疗应答的研究多集中在眼底形态学、遗传基因学等方面。本文将对影响 wARMD 不良应答反应的相关因素作一综述, 旨在为临床工作者制定更加精准的治疗及预后监测方案提供参考。

关键词: 湿性年龄相关性黄斑变性; 光学相干断层扫描; 血管内皮生长因子; 不良应答; 危险因素

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Research progress of related factors affecting poor response to wet age-related macular degeneration

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Abstract

• Wet age-related macular degeneration (wARMD) emerges as a primary contributor to irreversible vision impairment in the aging demographic. In clinical practice, anti-vascular endothelial growth factor (VEGF) therapies exhibit pronounced success in managing wARMD. However, in the actual clinical application, there are significant individual differences in the prognosis of anti-VEGF drug therapy, and some patients show poor response to the treatment, which may be related to the morphological differences of retinal layers in macular area, genetics, systemic conditions and other factors. It will help develop a more rational and individualized treatment plan to judge the prognosis of patients according to their different clinical manifestations in advance, so as to reduce overtreatment and the risk of retinal damage. In recent years, most studies on treatment response mainly focus on fundus morphology, genetics and so on. In this study, the relevant factors affecting adverse response to wARMD were reviewed, aiming to provide with more accurate treatment and prognostic monitoring programs for clinicians.

• **KEYWORDS:** wet age-related macular degeneration; optical coherence tomography; vascular endothelial growth factor; poor response; risk factors

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0 引言

年龄相关性黄斑变性 (age-related macular degeneration, ARMD) 是一类影响视网膜黄斑区的疾病, 是中老年人人群中引起视力损害的常见原因, 其中湿性年龄相关性黄斑变性 (wet age-related macular degeneration, wARMD) 主要以黄斑区新生血管 (macular neovascularization, MNV) 为主要特征, 因脉络膜内异常血管增生, 导致液体渗出, 损伤视网膜而引起视力障碍^[1-2]。在过去的 10 a, 抗血管内皮生长因子 (vascular

endothelial growth factor, VEGF) 药物的使用显著改善了 wARMD 患者的视力预后, 成为治疗的一线用药^[3-4]。虽然多数患者对治疗应答良好, 但仍有部分患者效果不佳, 表现为持续的视网膜下液 (subretinal fluid, SRF)、视网膜内液 (intraretinal fluid, IRF)、视网膜色素上皮层脱离 (pigment epithelial detachment, PED)、视网膜结构纤维化等, 严重影响视力^[5]。随着人口老龄化的加剧, 预计至 2040 年全球 ARMD 患病人数将达到 2.88 亿^[6]。因治疗成本高昂, 将给社会及个人带来沉重的经济负担, 故早期识别并分析应答不良患者的眼部病变特征, 探究影响治疗效果的相关因素, 制定个体化治疗方案显得尤为重要。本文将针对应答不良的相关因素及其研究进展进行综述, 为临床工作者提供参考。

1 抗 VEGF 治疗应答不良的判断标准

目前, 关于抗 VEGF 药物治疗应答的定义和分类尚未达成共识, 多数学者依据功能学及形态学检查等对应答不良作出如下判断标准: (1) 治疗 12 mo 后最佳矫正视力 (best corrected visual acuity, BCVA) 相较最初恶化超过 0.2 或下降超过 5 个字母; (2) 光学相干断层扫描 (optical coherence tomography, OCT) 显示黄斑区病变在治疗后仍进展或持续存在, 如中心凹视网膜厚度 (central retinal thickness, CRT) 较基线时增加 25% 或超过 100 μm 、伴有持续性或新的 IRF、SRF 等^[7-9]。

2 与治疗应答相关的 OCT 生物标志物

OCT 以快速和非侵入的优势为 wARMD 的诊断和治疗带来了革命性的变化, 现已用于预测和评估治疗反应并指导治疗。既往研究发现 OCT 的生物标志物与初始视力及治疗后视力改善有关, 具有进一步指导治疗进展的潜力。现在越来越多的研究集中在这些方面, 以提供更多的生物学标志物监测预后情况。

2.1 视网膜积液位置 研究发现, 病变的积液位置对治疗应答及视力预后具有重要影响, 病变处存在 IRF 者视力预后相对 SRF 者更差^[10-11]。Sadda 等^[10]发现在雷珠单抗治疗后第 12、24 mo, 残留 IRF 的患眼视力相对较差。病变局限于 SRF 的患者视力预后则相对于 IRF 者更好^[12]。另有长期研究表明, 对抗 VEGF 治疗无效的 SRF 患眼仍然保持视力提高^[13-14]。Jaffe 等^[15]在接受治疗后 5 a 的视力随访中发现, 有中心凹 SRF 的患眼视力相对更好。分析可能原因是 SRF 本身含有视网膜神经保护因子, 在光感受器中具有保护作用, 避免视网膜色素上皮 (retina pigment epithelium, RPE) 层和 MNV 的直接接触, 以及 SRF 对视网膜组织具有营养支持作用; 也可能是由于 SRF 相对于 IRF 存在的区域椭圆体带 (ellipsoid zone, EZ) 更完整, 从而视力更佳。视网膜积液位置对视力预后的影响还需要更多的讨论, 未来需要更多的样本量以及更细致的分组, 包括治疗的频率、视网膜积液的数量等进行视力预后评估。

2.2 视网膜下高反射物质 视网膜下高反射物质 (subretinal hyper-reflective material, SHRM) 指位于视网膜外部、RPE 层内部的高反光物质, 可由不同成分组织构成。既往研究指出基线 SHRM 的存在与基线视力具有相关性, SHRM 的范围越大, 预后视力越差, 可作为 wARMD 患者治疗预后的重要形态学标志^[15-17]。SHRM 内的纹理

变化可能与 wARMD 患眼的治疗反应显著相关^[18]。Kumar 等^[19]提出一些新的观点, 认为 SHRM 与 RPE 之间的间隙与视力的提高相关, 且 SHRM 中的高反射斑点影响视力预后。分析可能是由于 SHRM 和 RPE 之间的低反射层对应着一层液体, 可以保护 RPE, 而这些斑点可能代表对视力有害的炎症细胞。目前, SHRM 的存在与视力预后关系的机制尚未明确, 但对此生物学标志展开的相关研究为预后监测提供了一种新的研究方向。

2.3 视网膜外层结构紊乱 视网膜外层结构通常指外界膜 (external limiting membrane, ELM) 和 EZ, 是感光细胞层的高反射带, 被证明是视力预后的重要结构。完整的 EZ 可以作为良好视力结局的预测指标, 而 EZ 完整性缺失则表现相反^[20]。Ozer 等^[21]研究发现, 中心凹区 EZ 断裂长度如果超过 500 μm , 会严重影响视力预后, SRF 的存在与 EZ 和 ELM 中断长度具有密切联系, 是间接导致较差视力的因素。分析可能是由于 RPE 分离而发生的光感受器破坏。Woronkiewicz 等^[22]同样指出, EZ 和 ELM 的损伤程度与治疗后的 BCVA 及患者的视觉体验相关。也有研究指出, ELM 的完整性与 BCVA 之间的相关性高于 EZ^[23-24]。ELM 的破坏反映了光感受器核团的损伤, 从而造成严重的视网膜损伤, 而 EZ 只涉及节段, 因此即使在 EZ 界面消失后, ELM 也可作为视力增益的良好预测指标。EZ 和 ELM 的完整性反映了视网膜外层结构的损伤程度, 通过此形态学标志物, 将治疗预后与视网膜外层结构在 OCT 上的表现联系起来, 可以为更好地预测治疗应答反应提供参考, 但具体病理机制还需更进一步研究。

2.4 PED 的类型 PED 指 RPE 与 Bruch 膜内胶原层之间的分离, 可分为纤维血管型、浆液型、出血型和玻璃膜疣型, 其中浆液型和纤维血管型 PED 均与 wARMD 预后相关。研究报道, 浆液型 PED 患眼比纤维血管型 PED 患眼具有更好的视力预后^[25-26]。基线 PED 是 BCVA 改善的重要预测因子, 如果治疗前存在 PED, 患者的基线视力会更差, 以及在接受治疗后会有更少的视力改善^[27]。虽然有研究报告 PED 的存在可能预示着视力稍差, 但 de Massougnés 等^[28]研究指出视力主要受基线 BCVA 和 SRF 影响, 尽管基线存在 PED, wARMD 患眼在抗 VEGF 治疗 12 mo 后仍表现出良好的视力改善。目前对于 PED 与视力的关系仍然存在争议。PED 可能提示新生血管在出血发生之前已经存在, 而存在的新生血管对视网膜组织产生了一定的损伤; 也可能是因为 PED 损伤了 RPE、光感受器, 降低了其生理功能, 从而对视力预后产生影响。PED 对视力预后的影响还需要进一步探索, 未来的研究更应关注视力与 PED 形态特征的关系, 包括 PED 的高度、宽度、直径、面积等。

2.5 视网膜高反射点 视网膜高反射点 (hyper reflective dots, HRD) 是指在 OCT 中分散的且边界较清晰的、与 RPE 反射相同或高于 RPE 反射、直径 $>20 \mu\text{m}$ 且 $<50 \mu\text{m}$ 的高反射灶, 多存在于视网膜外层及 RPE 层附近, 也可分布在视网膜的各个层间, 其数量可作为 wARMD 和息肉样脉络膜血管病变视力预后的指标, 通过抗 VEGF 药物治疗可以减少 HRD 的数量, 对视力改善具有重要意义^[29-31]。Ota 等^[32]研究指出, 在 OCT 中高反射点与硬性渗出物的中心

凹下沉积有关。Coscas 等^[33]认为 HRD 是在疾病发展过程中炎症激活的小胶质细胞作用所致,可作为早期炎症反应的临床标志物。HRD 的存在可能是由于血-视网膜屏障的破坏引起的 SRF 渗出,渗出的液体伴有血液中的脂质和蛋白质物质,形成硬性渗出,最终破坏视网膜结构,降低视力。此外,HRD 的存在与光感受器的完整性相关,HRD 的数量越多,影响光感受器完整性的恢复,从而对治疗产生不良应答。关于 HRD 对治疗应答的潜在机制仍需要在未来的研究中进一步探讨与阐明。

3 与治疗应答相关的光学相干断层扫描血管成像参数

通过光学相干断层扫描血管成像(optical coherence tomography angiography, OCTA)可以更详细地观察 MNV 周围血管密度降低的区域,获取 MNV 的形态、范围等关键信息,对病变进行定性和定量分析,通过不同的微血管形态观察及预测疾病的活动性^[34-35]。如新生的未成熟的血管分支网对药物治疗表现出良好的应答反应,而粗大的血管网则应答欠佳^[36]。不同的 MNV 类型对治疗也表现出不同应答。Jia 等^[37]发现抗 VEGF 治疗 6 mo 后,2 型 MNV 和混合型 MNV 患者比 1 型 MNV 患者产生更好的应答反应,且 59% 对治疗应答良好的患者表现为 2 型 MNV 或混合型 MNV,76% 对治疗应答无充分反应者表现为 1 型 MNV。Mettu 等^[5]发现 2 型 MNV 患者治疗 1 a 后持续疾病活动率为 25%,而 1 型 MNV 患者为 41%。另有研究显示,小分支血管密度和血管长度与抗 VEGF 治疗后视力预后相关^[38]。然而,Cavichini 等^[39]认为 OCTA 上显示的新生血管并不总是预示着疾病的活动性,非活动性 MNV 在 OCTA 上可能也会有同样表现,OCTA 判断 wARMD 中 MNV 活动性的敏感性和特异性相对较低。

在临床工作中,眼底荧光素血管造影与 OCTA 都具有良好的眼底血管显影效果,但 OCTA 未能显示视网膜渗漏情况,对 MNV 活动性监测尚有欠缺之处,故需要结合 OCT 显示的视网膜厚度及层间积液等情况综合给予分析方能更准确地判断其活动性。在 OCT 上发现 MNV 活动征象之前,运用 OCTA 早期识别 MNV 活动性是未来研究的一个挑战。

4 与治疗应答相关的遗传学因素

ARMD 是一种具有遗传倾向的多因素疾病。目前已鉴定出与 ARMD 存在关联的遗传信息共有 52 个并分布在 34 个位点上,这些致病基因在控制免疫反应、炎症过程和视网膜稳态中发挥重要作用。ARMD 患者对治疗应答程度与这些位点的变异息息相关^[40]。有研究发现了可能与 ARMD 相关的遗传变异基因,如肝脂酶基因(LIPC)的一个变异体,其参与高密度脂蛋白胆固醇通路代谢^[41]。补体因子 H(complement factor H, CFH)基因、年龄相关性黄斑变性易感 2(ARMS2)和 VEGFA 中高风险等位基因与患者较低的发病年龄和抗 VEGF 药物治疗的低反应有关^[42]。同样,也有学者发现,CFH 基因多态性 T1277C 的变异与 wARMD 患者治疗后功能和形态反应延迟有关^[43]。近年研究发现遗传变异(ACAD10 位点)与转化为 wARMD 相关^[44]。Lorés-Motta 等^[45]发现 rs12138564(1:156,291,600)是与抗 VEGF 治疗 wARMD 反应相关的潜在遗传因子。Cobos 等^[46]首次发现,rs12603486、rs1136287

(SERPINF1)与 wARMD 患者接受雷珠单抗治疗后不良视力预后有关。然而,对于遗传基因在治疗应答方面的影响,有研究显示,应答组患者的视网膜厚度降低,视力显著增加,但对反应良好的遗传基因进行分析,却没有得到显著的结果^[47]。因此,为了避免遗传学研究中的不一致性,未来需要对治疗的基因表型进行更精细的分类,同时也需要更多的样本量,才能对该问题做出进一步详细探讨。

5 与治疗应答相关的全身因素

ARMD 的病因较为复杂,年龄、吸烟、高血压病史等常与 ARMD 的发病及治疗后的应答密切相关^[48]。既往研究发现,ARMD 的发病率均随年龄增长而增加,年龄是早期 ARMD 发病的危险因素之一^[49]。在 wARMD 发展过程中,与 43-54 岁人群相比,>75 岁的患者发生大玻璃膜疣、RPE 异常和地图样萎缩的发生率更高^[50]。年龄也成为影响患者治疗预后的重要因素。吸烟是 ARMD 重要的危险因素^[49]。Piermarocchi 等^[51]提出具有吸烟史的 ARMD 患者在接受治疗后,视力平均损失 13.9 个字母。分析可能是由于香烟中含有相关毒性化合物,可通过不同的生化途径对视网膜产生氧化应激,以及 RPE 细胞的炎症反应、脉络膜血管的血流变化产生病理效应。研究表明,wARMD 患者常伴有冠状动脉疾病和高血压等疾病,并影响视力预后^[52]。Piermarocchi 等^[51]发现,接受雷珠单抗治疗的 wARMD 患者中,无高血压患者的视力平均改善 3.0 ± 8.1 个字母,而高血压患者的视力平均改善 0.6 ± 9.1 个字母。此外,在 wARMD 发病前良好的血压控制可能会改善抗 VEGF 治疗的效果^[53]。分析原因可能是脉络膜血流减少刺激缺氧,并促进 VEGF 上调和新生血管形成。另有观点认为,在 wARMD 患者中未发现高血压的存在与玻璃体腔注射抗 VEGF 药物的不良预后存在相关性^[54]。

wARMD 是一种与全身基础情况密切相关的疾病,全身疾病与治疗预后相关的联系仍需进一步探索。全身情况的管理,解决潜在的危险因素,对治疗预后起着至关重要的作用。

6 与治疗应答相关的一般临床资料

发病病程长短及治疗时机与抗 VEGF 治疗应答不良相关。研究表明,延迟治疗 21 wk 及以上的患者与延迟治疗 7 wk 及以下的患者相比,治疗后视力预后更差^[55]。基线视力也是影响抗 VEGF 治疗应答不良的关键临床因素,基线视力越好,最终视力预后越好。研究发现,基线 BCVA 较差,会产生较差的视力结局,基线 BCVA 越好,每月视力改善越小,但最终视力结局较好,基线 BCVA 是最终视力结局的预测因素^[56]。一项回顾性研究同样表明,在抗 VEGF 治疗大于 2 a 的患者视力随访中,基线视力良好的患者在治疗随访过程中更有可能保持良好的视力,基线视力差的患者会获取更多的视力增益,但最终视力结局较差^[57]。分析可能是由于基线视力较好时接受治疗,从而获得的增益空间较小。对于一些瘢痕期的患者,因基线视力可能本身较差,治疗获益不会太理想。所以在临床中,基线视力较差的患者,往往在治疗上表现出应答不良现象,可以根据患者的基线视力及发病病程指导治疗。

7 小结与展望

抗 VEGF 治疗是目前治疗 wARMD 的一线方案,很多

患者在治疗后获得了良好的视力,但部分患者由于多方面因素的影响,对于治疗应答反应不佳。因此,探索影响治疗应答的相关因素显得至关重要。通过分析治疗前的相关影像学标志物,从而为患者制定最优的个体化治疗方案是未来的目标。此外,除了识别相关标志物外,还需要进一步通过 OCTA 分析不同类型 MNV 接受抗 VEGF 治疗前后的差异,探讨其与抗 VEGF 治疗反应的相关性,以指导 wARMd 患者的治疗效果评估及病情监测,最终达到预防或延缓疾病进展的目的。

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