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影响湿性老年性黄斑变性患者抗VEGF治疗应答的基线特征

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[摘 要] 玻璃体腔注射抗血管内皮生成因子(anti-vascular endothelia growth factor，VEGF)是目前湿性年龄相关性黄斑变性(wet age-related macular degeneration，wAMD)的标准治疗方案，但其治疗应答却存在个体差异。本文总结概括了遗传因素、基线视力、治疗时机、光学相干断层扫描成像(optical coherence tomography，OCT)及光学相干断层扫描血管成像(optical coherence tomography angiography，OCTA)上的影像学特征等对抗VEGF治疗应答有影响的临床基线特征，以期为选择治疗方案及预测预后提供依据。

[关键词] 湿性年龄相关性黄斑变性；抗血管内皮生长因子；治疗应答；影响因素

Baseline characteristics affecting the response of anti-VEGF therapy for wet age-related macular degeneration

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Abstract Current standard treatment of wet age-related macular degeneration (wAMD) is an intravitreal anti-vascular endothelia growth factor (anti-VEGF) therapy, but responses to treatment show large variability. This review summarizes genetic factors, baseline vision, treatment time, morphological characteristics shown on OCT and OCTA and other clinical baseline characteristics, which were associated with the response to the therapy, aiming to help select treatment regimen and predict the response to anti-VEGF therapy.

Keywords wet age-related macular degeneration; anti-vascular endothelial growth factor; treatment outcome; influencing factor

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抗血管内皮生长因子(anti-vascular endothelial growth factor，抗-VEGF)药物是治疗湿性年龄相关性黄斑变性(wet age-related macular degeneration，wAMD)的一线药物，它显著降低了wAMD患者诊断后2年内的致盲率[1]。但在临床实际应用过程中，部分wAMD患者对其应答不良[2-4]。在亚洲人群中，14.4%的wAMD患者在抗VEGF治疗后视力下降大于15个字母[5]。临床上主要通过视力预后及形态学预后评估抗VEGF治疗结局，其中应答不良表现为视力预后不佳，或者形态学上视网膜渗出水肿、出血及脉络膜新生血管(choroidal neovascularization，CNV)消退不明显[6]。抗VEGF治疗应答与患者的临床基线特征密切相关，因此，探寻影响wAMD患者治疗应答的基线特征，可以帮助预测抗VEGF治疗的疗效，并辅助制定更有针对性的、个体化的治疗方案。

1 临床一般资料

1.1 遗传因素

补体因子H(complement factor H，CFH)基因、高温需求蛋白A-1((high-temperature requirement A-1，HTRA1)基因、年龄相关性黄斑病变易感因子2(age-related maculopathy susceptibility 2，ARMS2)基因及*VEGF*基因，不仅参与了AMD的发病机制，还可能对抗VEGF治疗应答有影响。Arslan等[7]对wAMD药物遗传学相关研究进行了综合分析，发现上述基因对抗VEGF治疗应答的影响比重不同，其中CFH约占18%，ARME2约占13%，VEGF约占11%。另外Lazzeri等[8]发现白介素-8(interleukin-8，IL-8)基因rs4073的AA基因型与应答不良也相关。目前研究者还发现了对抗VEGF治疗应答可能有影响的新基因位点。Riaz等[9]通过全基因组关联研究发现：嗅觉受体家族52亚家族B成员4(olfactory receptor，family 52，subfamily b，member 4，OR52B4)基因与治疗应答相关，OR52B4基因在眼内视网膜、视盘、脉络膜均有表达，但其在AMD发病机制中的作用尚且不明确。而Lorés-Motta等[10]发现分子伴侣蛋白TCP1复合物亚基3(chaperonin containing TCP1，subunit 3，CCT3)基因可能可以作为预测视力预后的标志物，另外携带C10orf88 (chromosome 10 open reading frame88)或不协调的93同系物B1(uncoordinated 93 homolog B1，UNC93B1)罕见突变的患者治疗后视力分别下降30.6和26.5个字母，提示治疗应答不良。然而基因分型虽然是影响抗VEGF治疗应答的重要基线特征，对治疗应答具有预测作用，但其作用价值受到患者种族分布及治疗方案等差异的影响[7]。研究[11-12]发现：高加索人群中抗VEGF治疗应答与*CHF*基因密切相关，其中CHF Y402H CC基因型提示患者视力预后最差。然而在亚洲人种中，CHF基因与治疗应答相关性不强，相反*ARMS2 TT*基因型、*HTRA1 GG*基因型分别提示患者长期、短期视力预后差[13-14]。另外关于*VEGF*基因的研究[8,15-16]也发现，白种人中*VEGF rs3025000 TT*基因型、*VEGF-2 rs20171559 CC*基因型提示治疗应答良好[8,15]，但亚种人群中携带*VEGF rs833061 CC*基因型患者治疗应答更好。

AMD发病受多因素影响，关于遗传因素对抗VEGF治疗应答的影响尚且没有统一的结论，也需要更加丰富的研究以判断不同基因位点对治疗的影响程度，为临床治疗方案的选择提供可靠的依据。

1.2 基线视力

基线视力是影响wAMD抗VEGF视力预后至关重要的临床基线特征，也是目前临床决策必要的参考因素。患者基线视力越好，最终视力预后越好，尤其当患者基线视力大于55个字母时，视力预后极大可能大于69个字母[17]。但同时基线视力好的患者视力提升幅度反而更小[4,18]。其中基线视力小于20/100的患者治疗后视力提升幅度是大于20/100的患者的4.4倍[19]。在低视力患者(视力≤20/200)中，该发现也被证实：相较于基线视力大于20/400的患者，小于20/400的患者视力提升幅度更大[3]。研究[4,18-21]多以“天花板效应”来解释这一现象：抗VEGF治疗wAMD能达到的最佳视力有限，因此基线视力好的患者视力提升空间小，但是最终视力预后较基线视力差的患者仍然更好，这在临床上也可以帮助解释一部分基线视力良好但抗VEGF治疗后视力提升不明显的患者的困惑。

1.3 其他一般临床资料

抗VEGF治疗时机延误与应答不良相关。研究[22]发现：wAMD首发症状出现21周后开始抗VEGF治疗的患者，相较于仅间隔7周的患者，治疗后应答不良的风险提高了2.62倍。有部分学者[5,19]认为年龄大于70岁或者反复复发的患者对抗VEGF治疗应答更差。但年龄、性别等一般临床资料与治疗应答的相关性没有基线视力或影像学特征明确[23-24]。

2 影像学特征

2.1 光学相关断层扫描

光学相关断层扫描(optical coherence tomography，OCT)是wAMD诊断及随访的最主要影像学手段[25]，同时基线OCT上显示的一些视网膜形态学改变对患者视力预后有明确的预测价值。

2.1.1 视网膜囊样水肿

视网膜囊样积液(intraretinal cystoid fluid，IRC)、视网膜下积液是提示wAMD疾病活动的影像学指征[26]。其中IRC与视力预后差密切相关[27]。Sharma等[28]及Schmidt-Erfurth等[26]认为顽固性IRC(治疗3个月后仍不消退)是提示视网膜细胞出现不可逆凋亡的影像学指征，预示患者视力预后不佳。Kang等[29]进一步提出：内核层内的视网膜囊样积液(intraretinal cystoid fluid in the inner nuclear layer，INLc)与视力预后的相关性最为显著。基线伴有INLc意味着CNV病灶异常活跃，侵入性强，使内丛状层以及外丛状层屏障功能受损，液体渗漏可以快速扩散至内层视网膜内。因此基线INLc的出现可能提示疾病更活跃，预示视力预后更差。

2.1.2 外层视网膜完整性及影像学改变

外层视网膜中，视网膜外界膜(external limiting membrane retina，ELM)以及椭圆体带(Elilipsoid Zone)是决定wAMD患者视力预后的重要因素，其中ELM与视力预后关联更为紧密。ELM完整程度可以作为预测视力预后的独立因素，在所有相关因素中，其约占10%，意义甚至大于基线视力[24,30]。ELM起维持视网膜渗透压及蛋白梯度的作用，具有一定的屏障功能，对其下层椭圆体带有保护作用，并且在CNV形成的病理过程中，椭圆体带完整性受到破坏早于ELM层。因此ELM完整性破坏意味着椭圆体带早已受到损伤，光感受器功能受损严重，视力预后差极差[30]。

外层视网膜管形结构(outer retinal tabulation，ORT)是位于视网膜外核层，边缘呈椭圆形或圆形高反射、内部呈低反射或非均匀高反射的结构[31]。ORT被认为是光感受器完整性严重受损的标志，基线视力差、视网膜地图样萎缩、CNV病灶面积大，出现视网膜下高反射物质均与ORT出现相关[32]。基线OCT发现ORT与抗VEFG视力预后差相关，并且与远期视力预后差密切相关[33]。

2.1.2 高反射点

Akagi-Kurashige等[24]发现视网膜神经上皮层内的高反射点(hyperreflective foci，HF)与视力预后密切相关，然而超过80%的湿性AMD患者在随访过程中都会出现HF。因而Lee等[34]进一步发现HF数量与视力预后密切相关。Segal等[35]也证实，基线OCT上HF数量>20个才与视力预后相关，因此推测HF是由于炎症因子刺激而产生的视网膜神经上皮层内小胶质细胞，HF数量大意味着视网膜长期受到慢性炎症刺激，导致了不可逆的微小损伤，这些改变通过现有眼科检测手段难以观测到，因此即使视网膜结构看似得到恢复，但视功能仍无改善。

2.1.3 视网膜下高反射物质

wAMD患者OCT图像上一些位于视网膜神经上皮层下、色素上皮层内侧的病灶呈高信号，它们被称为视网膜下高反射物质(subretinal hyperreflective material，SHRM)，是由大量积液或硬性渗出集聚形成。Pokroy等[36]认为基线伴有SHRM是预测抗VEGF治疗长期视力预后的独立因素，SHRM持续存在的患者在治疗后出现视网膜瘢痕化的风险更大，并且不同形态的SHRM与视力预后相关性不同，其中边界清楚、反射信号更强的SHRM与视力预后不良相关性最大[37]。Roberts等[38]进一步提出：基线SHRM厚度及体积与视力预后负相关，尤其是治疗后SHRM厚度变化不明显的患者更早也更易出现视网膜瘢痕及萎缩，而SHRM基线面积、治疗后变化与视力预后均不相关。这可能与SHRM边缘是新沉积的物质有关，SHRM边缘对抗VEGF药物更敏感，因此相较于厚度，治疗后SHRM的面积变化在不同患者中无明

显差异，对患者视力预后预测价值不大[38]。另外Maruyama-Inoue等[39]根据SHRM组成成分，将其分为II型CNV型、纤维增殖型、视网膜下高反射渗出型(subretina hyperreflective exudation，SHE)，发现CNV型SHRM与视力预后差关联最密切。这可能与伴CNV型SHRM的患者椭圆体带损伤更严重有关。研究[39-40]发现：82.4%伴SHE的患者椭圆体带结构完整，但CNV型SHRM患者中仅有45.4%的人椭圆体带保持完整，因此其预后更差。另外SHRM形成使得RPE层与光感受器细胞连接断裂，对光感受器细胞造成不可逆损伤，可能阻断了正常的代谢循环，因此抗VEGF治疗后视力预后不佳[37,39]。

2.1.4 玻璃体黄斑交界面状态

Üney等[41]发现玻璃体黄斑粘连(vitreomacular adhesion，VMA)或玻璃体黄斑牵拉(vitreomacular traction，VMT)会影响wAMD患者的视力预后。玻璃体黄斑交界面正常的患者接受抗VEGF治疗后视力提升50个字母，伴有VMA/VMT的患者视力仅提升35个字母。异常的玻璃体黄斑交界面会产生牵拉力，直接作用于Miller细胞，并导致视网膜色素上皮细胞的拉伸变形。促进VEGF在内的多种炎症细胞因子分泌，最终诱发局部炎症并导致新生血管形成[42-44]。同时当视网膜受到牵拉时，组织细胞间液渗透压减小，血管内物质渗透至血管外，形成视网膜内的水肿，疾病也更加活跃[45]。另外研究[46-48]发现：伴VMA/VMT的wAMD患者的玻璃体腔内纤维发生变性，包裹VEGF在内的一些细胞因子，细胞因子被局限在视网膜结构中，固定水平的抗VEGF药物不足以中和过量的VEGF因子。因此抗VEGF治疗应答会受到异常玻璃体黄斑交界面影响。但同时研究[44-46]也发现：VMA/VMT仅影响患者的早期视力预后，当予以更频繁、更长久的治疗后，该影响会逐渐减弱，患者甚至可以达到与正常组一致的视力预后。未来也需要纳入更大的样本量，监测更全面的预后指标，对VMA/VMT对抗VEGF治疗应答的影响进行更深入的探讨。

2.2 OCTA上CNV病灶的形态特征

OCTA作为一种新型的非侵入的眼底影像技术，其灵敏性及准确性在wAMD的诊断、随访中与FFA相近[25,49-50]。OCTA可以清晰地显示CNV病灶的形态，对湿性AMD患者的CNV病灶进行定性分析。Timur等[51]将wAMD的CNV病灶人为地分为“树枝状(tree-like)”以及“线团状(loop-like)”。“树枝状”CNV为主干血管伴向同一方向发出的血管分支的病灶，“线团状”CNV为内部血管扭曲缠绕的环形病灶。研究[23]发现：“线团状”CNV病灶对抗VEGF治疗反应更好。另外有研究将CNV根据形状分为海葵型、水母型、类肾小球状、树枝样、血管吻合环等，但目前由于CNV形状变化较大，对CNV形态的定义和分类分歧较大，没有较为统一的标准，因此以CNV病灶形状作为预测治疗反应的指征并不准确。反而研究CNV病灶的血管组成对抗VEGF治疗更有价值。

2.2.1 OCTA上CNV病灶的血管组成

OCTA能显示视网膜及脉络膜不同层次的血管网，可以获取更丰富的CNV病灶的信息，赵治等[52]认为OCTA有望成为“活体血管生物标志物”。有研究[53-55]应用OCTA对CNV病灶在抗VEGF治疗中的变化进行了探究，发现抗VEGF药物对CNV血管进行了“裁剪”：治疗过程中，CNV病灶不断地重复着毛细血管萎缩-新生血管芽萌出的血管重构过程，这一过程也被称为“动脉化”或“正常化”。抗VEGF治疗后，CNV内的毛细血管成分及小血管吻合消退，残留的主干血管灌注增加，血管扩张，管径增粗，走形更僵直，血管逐渐成熟，而成熟的血管内皮被覆周细胞，对抗VEGF治疗出现抵抗[56-57]。因此基线CNV病灶呈现成熟血管形态与CVN病灶对抗VEGF治疗应答不良密切相关，相反地基线CNV病灶内毛细血管分支丰富、分支血管网复杂、血管末端吻合丰富、有外周血管弓形则提示病灶活跃且不成熟，这些指征与CNV病灶对抗VEGF治疗应答良好相关[23,56]。

2.2.2 OCTA的定量分析

OCTA可测量CNV病灶血流面积、血管密度、脉络膜血管密度等参数，并对CNV病灶进行客观定量分析[58]。Faatz等[49,59]发现：经抗VEGF治疗后，CNV病灶面积、血管总长度及毛细血管数量均显著下降，并且其变化幅度与治疗后视力预后及形态学上视网膜结构的预后正相关。同时Lee等[60]发现视乳头旁脉络膜毛细血管密度低与视力预后差可能相关，认为脉络膜灌注低可能提示wAMD患者病程更长，视网膜渗出水肿的形成与VEGF因子关系不密切，并且这类患者眼内VEGF

因子表达水平稳定，抗VEGF药物很难有效降低其浓度，这可能是其视力预后差的原因。随着OCTA成像及算法的进步，可以通过分形维数(fractal dimension，FD)评估CNV病灶血管构成复杂程度，FD值高提示血管网构成更复杂，CNV病灶较活跃[61]，且FD值与视力及视网膜结构预后均正相关[59]。另外孔隙度分析(lacunarity)也被引入分析CNV血管网的均质程度，但与预后的相关性需要进一步探讨[62]。由于OCTA成像原理是检测一定血流速度范围内的血流信号，当血流速度过慢时血管会被“遗漏”，其测量的参数与实际可能存在差异[49]，因此评估OCTA定量参数对治疗应答的影响时，还需要结合OCT、眼底照相等其他眼科影像学的结果。

4 结语

抗VEGF是目前wAMD的一线治疗方案，但临床应用中，由于患者的个体差异、治疗方案等因素的影响，患者的治疗应答各不相同。因此为了制定更加科学有效的个体化治疗方案，探索与功能、结构预后密切相关的基线特征就显得尤为重要。目前遗传因素、基线视力、起始治疗的时机影像学等临床基线特征均被证实与抗VEGF治疗应答相关。而随着OCTA的分辨率及算法不断进步，其为检测CNV病灶提供了新的定性、定量的指标。OCTA显示的成熟血管形态特征是临床上抗VEGF治疗抵抗的关键机制之一。然而OCTA显示的CNV病灶特征及定量参数与OCT上出现渗漏等疾病活动特征之间的关联尚且不明朗，需要进一步的研究探索，以为临床治疗提供更为客观的预测治疗应答相关的基线特征。

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