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【述评】

重视黄斑水肿的病因、治疗及预防△

李筱荣　周怀蔚

作者简介:李筱荣,男,1964年8月出生,天津人,博士。政府特殊津贴专家、教授、博士生导师。天津医科大学眼科医院院长、眼视光学院院长、眼科研究所所长。中华医学会眼科学分会专家会员,中华医学会眼科学分会眼底病学组委员,天津市医学会眼科学分会副主任委员。发表专业论文230余篇,包括SCI论文55篇,国家级专利6项;主编、副主编、参编专著26部。联系电话:18622818042;E-mail:xiaorli@163.com;ORCID:0000-0001-6855-7671

About LI Xiao-Rong: Male, born in August, 1964. Medical doctor. Government special allowance expert, professor, doctoral supervisor. Director of Tianjin Medical University Eye Hospital, School of Optometry and Ophthalmology, Eye Institute. Expert member of Ophthalmology Branch of Chinese Medical Association, member of Eye Fundus Group of the Ophthalmology Branch of the Chinese Medical Association, vice chairman of Ophthalmology Branch of Tianjin Medical Association. Tel: 18622818042; E-mail: xiaorli@163.com; ORCID: 0000-0001-6855-7671

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作者单位:300384　天津市,天津市视网膜功能与疾病重点实验室,天津医科大学眼科医院视光学院,天津医科大学眼科研究所
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From the *Tianjin Key Laboratory of Retinal Functions and Diseases, Tianjin Medical University Eye Hospital, School of Optometry and Ophthalmology & Eye Institute, Tianjin* 300384, *China*

Special attention to the cause, treatment and prevention of macular edema

LI Xiao-Rong, ZHOU Huai-Yu

【Abstract】 The pathophysiology of macular edema (ME) is complex, and the main structural changes are the destruction of the blood-retinal barrier, retinal vein occlusion, diabetes, uveitis, surgery and some drugs can be secondary to macular edema. Different pathogenesis of ME causes different pathogenesis, and vascular endothelial growth factor (vascular endothelial growth factor, VEGF) and inflammation are the main pathogenic pathways. Anti-VEGF as a first-line treatment of ME, although to some extent improve the efficacy of ME, there are still cases of anti-VEGF resistance. How to choose a personalized solution suitable for patients in anti-VEGF, hormone therapy, laser therapy, surgery, non-steroidal anti-inflammatory drugs and traditional Chinese medicine has become a difficult point of treatment. Meanwhile, it is also the current focus to strengthen the education of high-risk groups, actively carry out screening work, and prevent it.
【Key words】 macular edema; diabetic macular edema; retinal vein occlusion; vascular endothelial growth factor; inflammation

【摘要】 黄斑水肿(macular edema, ME)的病理生理较为复杂,主要结构改变是血-视网膜屏障的破坏,视网膜静脉阻塞、糖尿病、葡萄膜炎、手术以及一些药物均可继发ME。不同病因导致的ME发病机制不同,其中血管内皮生长因子(vascular endothelial growth factor, VEGF)和炎症为主要的致病途径。抗VEGF作为ME的一线治疗,虽然一定程度上提高了ME的疗效,但尚存在对抗VEGF耐药的病例。如何在抗VEGF、激素治疗、激光治疗、手术、非甾体抗炎药物以及中药等诸多治疗措施中选择适合患者的个性化方案成为治疗的难点。同时,加强对高危人群的宣传教育、积极开展筛查工作并做好预防,亦是当前的重点。
【关键词】 黄斑水肿;糖尿病性黄斑水肿;视网膜静脉阻塞;血管内皮生长因子;炎症
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黄斑水肿(macular edema, ME)是指血-视网膜屏障(blood-retinal barrier, BRB)破坏后液体在黄斑区视网膜内积聚[1]。黄斑作为决定视功能的重要部位,其结构的破坏必然引起功能的紊乱,临床上患者常表现为视力下降、视物变形或视物遮挡。随着抗血管内皮生长因子(vascular endothelial growth factor, VEGF)时代的到来,治疗效果得到很大提升。然而,临床上对抗VEGF治疗不敏感的病例不胜枚举。因此,临床医师只有深入理解ME的发病机制及病理生理,全面了解其不同病因及危险因素,熟练掌握当前不同治疗措施的适应证及优缺点,才能准确诊断、精准治疗,为患者提供个性化的治疗和随访方案。

1　深入认识ME的不同病因

视网膜色素上皮(retinal pigment epithelial, RPE)细胞间和视网膜毛细血管间的紧密连接损伤进而导致BRB破坏,液体积聚在黄斑处形成水肿[2]。光学相干断层扫描(optical coherence tomography, OCT)因其非侵入性、可重复性和敏感性已成为ME诊断的标准工具。荧光素眼底血管造影(fundus fluorescein angiography, FFA)和吲哚菁绿血管造影(indocyanine green

angiography,ICGA)有助于研究黄斑和相关血管,检测缺血区域或脉络膜新生血管等并发症,提供有关病因的信息,是评估治疗反应所必需的[3]。按照 ME 发生的病理生理过程,可以将其分为以血管损伤为主要损害的 ME 和以炎症为主要损害的 ME。

1.1 以血管病变为主要损害的 ME 一些全身因素(如高血压、糖尿病、血脂代谢异常)和眼部因素(如青光眼)会造成血管内皮细胞损伤,血流动力学改变,由此导致视网膜缺血缺氧,VEGF 表达上调:(1)VEGF 调节血管紧张素和 VE-钙黏蛋白的黏附和表达,其与受体的相互作用导致细胞内磷酸化级联,紧密连接蛋白降解,血管通透性增强,液体由血管内向组织间隙渗漏,细胞外间隙扩大,液体积聚[2];(2)诱发新生血管,新生血管由单层的血管内皮细胞组成,无血管内皮紧密连接,从而加剧液体渗漏。这些改变进一步诱发炎症,参与到 ME 的发生发展中。这类 ME 主要有视网膜静脉阻塞继发黄斑水肿(macular edema secondary to retinal vein occlusion,RVO-ME)、糖尿病性黄斑水肿(diabetic macular edema,DME)、口服避孕药(oral contraceptive pill,OCP)继发的 ME 以及芬戈莫德继发的 ME 等。

RVO 在一般人群中发病率为 0.08%,在 65 岁以上人群中为 0.92%[4]。The Beijing Eye Study 对中国成年受试者视网膜静脉阻塞(retinal vein occlusion,RVO)和相关因素的 10 a 发病率研究发现,在所有 RVO 眼中,37% 检测到 ME,其中 30% 为视网膜分支静脉阻塞[5]。RVO-ME 的发病机制目前尚未完全阐明,多认为是由于 RVO 后,毛细血管后小静脉难以将液体通过毛细血管网转输至前静脉导致回流障碍,视盘总静脉干处的血压较大,这部分液体难以泵回,故直接存留于视网膜间隙。

2017 年,国际糖尿病联盟(international diabetes federation,IDF)公布第 8 版糖尿病版图,全球范围内接受调查的患者中 7.6% 被诊断出患有 DME[6]。长期高血糖导致视网膜神经血管单元的损伤,BRB 破坏累及黄斑时,出现黄斑区的出血甚至缺血,在 FFA 或 OCTA 检查中,多可以观察到黄斑区内毛细血管网的部分闭锁,表现为中心凹毛细血管拱环扩大[7]。

一些药物可引起全身代谢紊乱,诱发 ME:(1)OCP 的青年女性者易患 RVO,高达 66.0%[8-9]。OCP 可升高纤维蛋白原与因子Ⅶc 的水平,使血液处于高凝状态;还可引起血压一定程度升高,血清低密度脂蛋白(low density lipoprotein,LDL)升高,高密度脂蛋白(high density lipoprotein,HDL)降低,而高血压和高脂血症是青年 RVO 的主要危险因素[9-10];(2)芬戈莫德作为一种治疗复发缓解型多发性硬化症的新型免疫抑制剂,是 G-蛋白偶联受体 S1P1 和 S1P3-5 的高亲和力配体[11]。长期服用可使 S1P1 受体表面表达减少,导致了 S1P1 的平衡向 S1P2/S1P3 信号的转移,而 S1P2/S1P3 激活则增加内皮屏障通透性[12]。

1.2 以炎症为主要损害的 ME 炎症在 ME 的发病中亦占有一席之地[13-14]。小胶质细胞作为视网膜固有免疫细胞,静息状态下呈分支状,位于视网膜内层,起免疫监控作用。局部微环境改变时,小胶质细胞激活,转变为阿米巴状,迁移至应激部位,释放大量炎性介质,促进白细胞迁移、细胞黏附和血管通透性增加[15-16]。正常情况下,Müller 细胞贯穿视网膜全层并包绕在视网膜血管表面,维持视网膜内水-离子平衡,炎症可以引起 Müller 细胞功能异常,导致细胞内液体清除减少,造成 ME。在 ME 患者的房水及玻璃体液中发现 IL-1、IL-6、IL-8、单核细胞趋化蛋白-1(monocyte chemotactic protein-1,MCP-1)和肿瘤坏死因子 α(tumor necrosis factor-α,TNF-α)水平升高,这些因子在炎症和血管通透性增加方面起重要作用[17-18]。另外,炎症促进 VEGF 的表达,激活下游信号通路,加重血管渗漏[19]。炎症在葡萄膜炎黄斑水肿(uveitic macular edema,UME)和眼部手术后黄斑囊样水肿中起主要作用。

葡萄膜炎患者中白细胞分泌促炎的细胞因子和金属蛋白酶诱导紧密连接蛋白磷酸化,通过表达多种黏附蛋白(选择素和细胞间黏附分子-1)以及整合素的构象变化,促进白细胞向视网膜迁移并与活化的内皮细胞黏附。除促进 BRB 分解的因子外,还包括促炎的细胞因子,如 TNF-α、IL-1、转化生长因子-β、血管紧张素Ⅱ、腺苷、组胺以及葡萄糖等。在中度葡萄膜炎患者房水中还发现 IL-6 和 IL-8 水平增高[3,20-21]。

眼科手术往往对眼内稳态造成一定程度的干扰,诱发炎症反应。人工晶状体眼黄斑囊样水肿(pseudophakic cystoid macular edema,PCME)[22]和后巩膜加固术继发 ME[23]较为常见,年龄、糖尿病、RVO 史、后囊破裂、葡萄膜炎、视网膜前膜等多种危险因素参与其发生[24]。主要病因被认为是炎症介质(特别是前列腺素 E_2)增加、视网膜内促炎基因和蛋白上调,破坏了血-房水屏障和 BRB[25]。

2 个体化精准治疗方案的选择

由于 ME 的发病机制复杂,如何按照不同病因、患者特征及体质精确选择治疗方案为患者提供个体化的治疗,已成为当前 ME 治疗的研究重点。目前针对 ME 的治疗方法主要有抗 VEGF、激素、激光光凝、手术、非甾体抗炎药物和中药。ME 的治疗时机尤为重要,黄斑区长期水肿状态可能引起感光细胞损伤,视网膜缺血及萎缩,最终导致永久性视力丧失。早期治疗可避免感光细胞受损及黄斑区视网膜结构改变,有效挽救视力。对于持续性 ME,水肿减轻并不能带来相应的视力改善,但可维持现有视力[20]。

2.1 根据不同病因优先选择 根据病因不同,在选择治疗方案时应审证求因:(1)需要注意详细询问患

者的用药史,对于一些可能继发 ME 的药物,应建议停用;(2)RVO-ME、DME 首选抗 VEGF 治疗,降低玻璃体内 VEGF 水平,可以恢复黄斑形态,提升视力;(3)糖皮质激素作为治疗 UME 的一线用药,能积极有效地控制炎症,促进 ME 的消退。治疗慢性顽固性 UME,可加用环孢素、甲氨蝶呤、硫唑嘌呤、麦考酚酸酯等免疫抑制剂[20]。

抗 VEGF 药物作用时间较短,需重复注射,增加了玻璃体内注射并发症发生的概率,同时,其作用途径较为单一。而激素治疗的并发症(眼压升高、白内障形成和纤维化)也不容忽视。Ozurdex 作为糖皮质激素的最新用药方式,相比 IVTA,并发症发生率较低。尽管如此,玻璃体切割术后合并晶状体后囊破裂的患者应谨慎选择,存在植入物进入前房的可能。因此,转换治疗和联合治疗被提出,旨在获取相同视力获益的同时减少患者的经济负担。

2.2 转换治疗

2.2.1 不同抗 VEGF 药物之间的转换 目前临床常用的抗 VEGF 药物分为两类:单抗类和融合蛋白类。Bahrami 等[26]对 43 例 DME 患者从单抗类转换为融合蛋白类治疗后,发现解剖学和功能学均得到良好改善。Rahimy 等[27]的研究却表明,虽然这样的转换能导致显著的解剖学改善,但视力的改善趋势无统计学意义。一项针对 RVO-ME 的 Meta 分析指出,从单抗类转换为融合蛋白类可改善继发于 RVO 的持续性 ME,但视觉恢复的可能性存在限制[28]。有必要进行前瞻性随机试验进一步研究,以验证这些发现。

2.2.2 抗 VEGF 与激素之间的转换 临床研究发现,约有 30% ME 患者对抗 VEGF 反应欠佳[29],一些学者将抗 VEGF 治疗转换为 Ozurdex 后发现,患者最佳矫正视力(best corrected visual acuity,BCVA)改善,注射次数和并发症的发生率明显减少[30-31]。转换治疗的指征各不相同,较多的方案为接受抗 VEGF 治疗≥3 次,视力无改善且持续有 ME[32-34]。同样,Pielen 等[30]对抗 VEGF 药物和 Ozurdex 的转换治疗进行了回顾性研究,发现由抗 VEGF 治疗转换为 Ozurdex 治疗的患者,BCVA 平均可改善 4 个字母,而 Ozurdex 治疗无效的患者换用抗 VEGF 药物治疗,BCVA 无明显改善。由 Ozurdex 治疗转换为抗 VEGF 治疗的情况多是由于激素的眼部并发症导致[4]。因此,早期识别对抗 VEGF 治疗反应差的患者并及早转换为 Ozurdex 治疗有助于改善预后。

2.3 联合治疗

2.3.1 不同药物之间的联合治疗 考虑到 ME 的发病中 VEGF 升高和炎症作用同时存在,另外一些学者探讨了抗 VEGF 药物联合激素的治疗方案。很多临床研究均已证实,抗 VEGF 联合曲安奈德玻璃体内(或后 Tenon's 囊下)注射治疗 DME 及 RVO-ME 可以减少所需的注射次数[35-36]。但曲安奈德的作用时间较短,且并发症发生率很高。

Singer 等[37]对 RVO-ME 患者进行了抗 VEGF 和 Ozurdex 的组合治疗(每周期治疗包括抗 VEGF 药物 1 针,2 周后 Ozurdex 1 针),在 2 a 治疗期间,所有患者接受组合治疗的时间间隔为(135.5 ± 36.4)d,显著降低了注射负担。同时,Singer 等[37]还研究了序贯疗法(即贝伐单抗 1 针,2 周后 Ozurdex 1 针,后续酌情贝伐单抗治疗)对 RVO-ME 的疗效,结果发现约 70% 患者在治疗后 4 ~ 5 个月需再次接受贝伐单抗注射;终点时,患者 BCVA 平均提高 16.8 字母,提示序贯治疗后再治疗间隔明显延长,且视力改善显著[38]。然而,Maturi 等[39]对 30 例 DME 患者组合治疗(贝伐单抗治疗后 1 个月接受 Ozurdex,随后每隔 4 个月再注射 Ozurdex,并酌情贝伐单抗治疗)的研究结果显示,组合治疗与单纯贝伐单抗相比,平均视力变化相似,虽然补充注射减少 3 针,但这需要平均 2.1 次 Ozurdex 注射。目前联合治疗的方案仍需要进一步探索,如何根据 ME 的发病过程选择合适的时机进行药物的组合是重点,尽管房水和玻璃体液炎性因子和 VEGF 的检测提供了很大支持,但是这种有创检查广泛应用于临床仍困难重重,探索新的更有临床意义的生物标志物迫在眉睫。

2.3.2 药物与其他治疗手段的联合治疗 格栅样激光光凝联合药物治疗可减少患者的平均注射次数,并维持治疗的短期和长期结果,降低治疗成本[40-41]。近年来,荧光造影指导的微脉冲激光治疗也开始得到认可。有研究认为,微脉冲激光对黄斑的损伤更小,并得到了具有积极意义的数据[42]。另外,当存在严重的玻璃体黄斑牵拉时,药物联合扁平部玻璃体切除能够帮助部分对光凝和抗 VEGF 治疗无效的患者提高视力。然而,对基线视力较好的患者,玻璃体切割术改善视力的效果有限。此外,Morizane 等[43]和 Abdel Hadi[44]评价了视网膜下平衡盐溶液(balanced salt solution,BSS)联合常规玻璃体切割术治疗 DME 的疗效,试验结果表明,该方法对抗 VEGF 治疗耐药的弥漫性 DME 消退和视力提高均有较好的效果。

2.4 辅助治疗

非甾体抗炎药物(non-steroidal anti-inflammatory drugs,NSAID)是环氧合酶(cyclooxygenase,COX)的有效抑制剂,COX 是炎症途径中的关键催化剂。因此可用来减少术后炎症,预防和治疗手术继发的 ME。新的非甾体抗炎药物(溴芬酸和奈帕非那酸)具有更大的角膜穿透性,在临床前的研究中,被证明在包括视网膜在内的眼部组织中有较高的浓度[45]。

中医理论认为,黄斑属脾。脾主运化,主升清,黄斑水肿,当责之于脾。脾气虚弱,运化不健,水湿内停,发为水肿[46]。故 ME 的治疗原则为“补气利水为主,活血补血为辅”,药物使用频次前 10 位的单味药物为茯苓、泽泻、黄芪、当归、川芎、猪苓、生地

黄、白术、丹参、车前子[47]。此外,一些中药制剂如复方血栓通、芪明颗粒可以作为治疗 ME 的临床辅助用药[48]。

3 ME 的预防

ME 的预后较为复杂,受多重因素影响。视网膜血流灌注,特别是黄斑区微循环情况与视力预后明显相关,缺血型尤其是黄斑区浅、深层毛细血管网破坏严重的患眼视力预后差。此外,视网膜各层结构的完整性与视力预后密切相关,中心凹下椭圆体带、外界膜完整的患眼视力预后好;基线视力好、治疗早期反应好以及年轻、治疗及时的患眼视力预后较好[49]。由此可见,ME 的预防显得尤为重要。目前文献中报道 ME 的危险因素主要有年龄、吸烟、饮酒、高血压、高血脂、高血糖[50]、高同型半胱氨酸血症[51-54]以及 OCP 等。因此,应该加强宣传,对已具备一些危险因素的人群,要重视控制全身危险因素,如合理控制体质量、糖尿病饮食、戒烟及适当运动等。同时,还应积极开展眼底筛查,根据欧洲视网膜专家协会(European Society of Retina Specialists Congress,EURETINA)、美国眼科协会(American Academy of Ophthalmology,AAO)和中华医学会眼底病学组发表的指南,建议无糖尿病视网膜病变患者每1~2 a 行 1 次检查;轻度非增殖期视网膜病变患者每年 1 次,中度非增殖期病变患者每 3~6 个月 1 次;重度非增殖期病变患者每 3 个月 1 次;对发现的问题,给予积极有效的治疗,以达到最佳的视力结果。

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