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【应用研究】

# 非增生型糖尿病视网膜病变超广角眼底彩色照相与眼底自发荧光图像特征分析

龙婷 杜磊 赵秋雅 邢怡桥

作者简介:龙婷,女,1993年4月出生,在读硕士研究生。主要研究方向:玻璃体视网膜疾病。联系电话:13006363830; E-mail: longting7@163.com; ORCID:0000-0002-8118-4117

About LONG Ting: Female, born in April, 1993. Postgraduate student. Tel: 13006363830; E-mail: longting7@163.com; ORCID:0000-0002-8118-4117

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本文编辑:方红玲

作者单位:430060 湖北省武汉市,武汉大学人民医院眼科中心

通讯作者:杜磊, E-mail: du-lei@126.com; ORCID: 0000-0002-4434-6586

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From the Department of Eye Center, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei Province, China

Responsible author: DU Lei, E-mail: du-lei@126.com; ORCID:0000-0002-4434-6586

## Analysis of ultra-wide-field fundus fluorescein angiography and fundus autofluorescence imaging in nonproliferative diabetic retinopathy

LONG Ting, DU Lei, ZHAO Qiu-Ya, XING Yi-Qiao

**[Abstract] Objective** To analyze image features of ultra-wide-field fundus fluorescein angiography and fundus autofluorescence (FAF) in patients with nonproliferative diabetic retinopathy (NPDR). **Methods** Totally 40 patients (80 eyes) who were diagnosed as NPDR respectively accepted ultra-wide-field fundus fluorescein angiography and FAF imaging using nonmydriatic optomap panoramic 200Tx, all images were analyzed to obtain imaging characteristics and positive rates. **Results** The image quality of ultra-wide-field fundus fluorescein angiography and FAF were much alike on peripheral retina. Imaging of tiny angioma and retinal hemorrhage were enhanced on FAF in different types of exemplary retinopathy, which contributed to the diagnosis of subtle lesions. Resolution of FAF was not adequate to diagnose retinal exudates. Recent photocoagulated spots were clearly displayed on both examinations, but prudent consideration for distant photocoagulated spots was recommended because they were not distinguishable from retinal hemorrhage. **Conclusion** Ultra-wide-field fundus fluorescein angiography displays clear imaging on peripheral retina and provides intuitive retinal images. FAF reveals subtle changes on retina, including metabolism of retinal pigment epithelial cells. These two modes complement each other and provide more advanced assistance for the diagnosis, stages and treatment of NPDR.

**[Key words]** non-proliferative diabetic retinopathy; ultra-wide-field fundus fluorescein angiography; fundus autofluorescence

**【摘要】 目的** 分析非增生型糖尿病视网膜病变(non-proliferative diabetic retinopathy, NPDR)超广角眼底彩色照相与眼底自发荧光(fundus autofluorescence, FAF)的图像特征。**方法** 使用欧堡全景200激光扫描检眼镜对40例(80眼)NPDR患者进行免散瞳模式下的超广角眼底彩色照相及FAF检查,对所有图像进行分析,得出两种模式下NPDR眼底改变的图像特征及阳性率。**结果** 超广角眼底彩色照相和FAF的图像质量基本一致,均能反映周边部视网膜的情况。在各种典型的眼底病变中,极其微小的血管瘤以及点片状视网膜出血的显影在FAF上有增强,有助于细微病变的诊断。渗出在FAF上的显影并不明显,分辨率不够。视网膜新鲜性光凝斑在两种模式检查上均显影清晰,陈旧性光凝斑在FAF上易与出血混淆,应谨慎诊断。**结论** 超广角眼底彩色照相图像清晰,周边部显示好,可以提供直观的视网膜图像;FAF可以观察到组织结构的细微改变及视网膜色素上皮细胞的代谢情况。两种模式相辅相成,能为NPDR的诊断、分期和治疗提供更好的帮助。

**【关键词】** 非增生型糖尿病视网膜病变;超广角眼底彩色照相;眼底自发荧光

**【中图分类号】** R774

糖尿病视网膜病变(diabetic retinopathy, DR)是一种慢性、进行性、潜在危害视力的视网膜微血管病变,与持续高血糖等相关。预计到2030年,全世界将有大约3.6亿人罹患糖尿病<sup>[1]</sup>,我国目前糖尿病患病率约为9.7%<sup>[2]</sup>。早期称为背景期或非增生型糖尿病视网膜病变(non-proliferative diabetic retinopathy, NPDR),随着新生血管生成和纤维组织增生到达晚期,称为增生型糖尿病视网膜病变(proliferative diabetic retinopathy, PDR)。NPDR眼底可见微血管

瘤、出血斑、硬性渗出、棉絮斑、黄斑水肿、视网膜微血管异常等。眼底检查可以直接观察到视网膜脉管系统和相关病理改变<sup>[3]</sup>。

目前,DR的诊断主要依靠直接、间接眼底镜,眼底彩色照相,荧光眼底血管造影(fundus fluorescein angiography, FFA)、光学相干断层扫描(optical coherence tomography, OCT)和光学相干断层扫描血管成像(optical coherence tomography angiography, OCTA)等检查方法。近年来,超广角眼底彩色照相技术作

为一项新兴的非侵入性检查技术,在免散瞳情况下,成像范围约 200°,可发现既往不能发现的周边部视网膜病变,已广泛用于 DR 的筛查与诊断。自发荧光可以反映脂褐质的含量与分布情况,评价视网膜色素上皮 (retinal pigment epithelial, RPE) 细胞的代谢状态,提供更多的视网膜病变信息。本研究对 40 例 (80 眼) NPDR 患者超广角彩色眼底照相和眼底自发荧光 (fundus autofluorescence, FAF) 图像特征进行分析,现将结果报告如下。

# 1 资料与方法

**1.1 一般资料** 回顾性分析研究。收集 2017 年 1 月至 2018 年 3 月就诊于武汉大学人民医院眼科并确诊为 NPDR 的患者 40 例 80 眼,其中男 23 例 (46 眼)、女 17 例 (34 眼),年龄 38 ~ 80 岁,平均 53.2 岁。

排除标准:(1)有眼部外伤史、眼部手术史,葡萄膜炎、青光眼等眼部疾病;(2)屈光间质混浊,影响眼底观察;(3)伴有全身其他重大疾病,尤其是有眼部并发症的相关疾病;(4)仅获得超广角眼底彩色图像或者 FAF 图像者。该研究已获得武汉大学人民医院伦理委员会批准。

**1.2 方法** 本研究选择的 NPDR 患者,从超广角眼底彩色照相和 FAF 上均呈现多样化的眼底改变,同一眼底也存在多种病变。本研究分别记录了超广角

眼底彩色照相和 FAF 的各种 NPDR 眼底典型特征的阳性例数,并对比两种检查的阳性率。所有患者均接受了视力、裂隙灯、前置镜、超广角眼底彩色照相及 FFA 检查。检查前先用前置镜大致判断患者的眼底情况。应用欧堡全景 200 激光扫描检眼镜 (Optos SLO),不必散大瞳孔,单次扫描获得 200°范围内的眼底彩色照相和 FAF 图像。

**1.3 统计学方法** 本研究利用 SPSS 25.0 进行统计学分析,对两种检查模式下的阳性率进行  $\chi^2$  检验。 $P < 0.05$  为差异有统计学意义。

# 2 结果

**2.1 一般结果** 在超广角眼底彩色照相中,微血管瘤、出血斑、渗出以及新鲜、陈旧性视网膜光凝斑的阳性眼数分别为 37 眼、59 眼、59 眼、28 眼与 32 眼。而在 FAF 图像中,微血管瘤、出血斑、渗出以及新鲜、陈旧性视网膜光凝斑的阳性眼数分别为 39 眼、60 眼、47 眼、28 眼与 24 眼。在视网膜陈旧性光凝斑的显影中,眼底彩色照相效果更佳 ( $P = 0.047$ ),而对于渗出这一眼底表现,则是眼底彩色照相更有优势 ( $P = 0.044$ )。尽管极其微小的血管瘤以及点片状视网膜出血的显影在 FAF 上有增强,有助于细微病变的诊断,但差异均无统计学意义 (均为  $P > 0.05$ )。

**2.2 典型特征的眼底图像展示** 本研究中具有典型特征的眼底图像见图 1 和图 2。

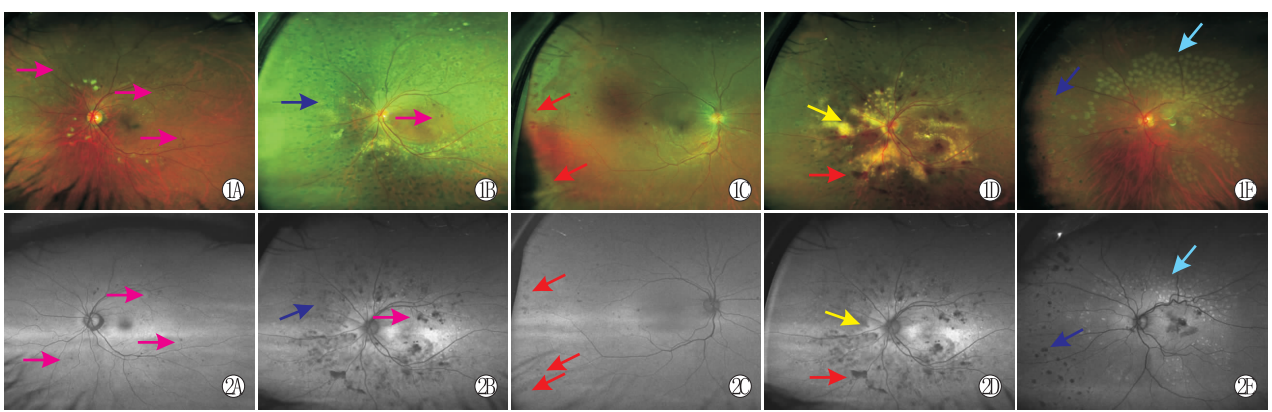


图 1 NPDR 患者超广角眼底彩色照相图像。图 2 NPDR 患者 FAF 图像。图 1A、图 2A 粉色箭头指示眼底微血管瘤;图 1B、图 2B 粉色箭头指示眼底微血管瘤,深蓝色箭头指示陈旧性光凝斑;图 1C、图 2C 红色箭头指示眼底周边部出血斑;图 1D、图 2D 红色箭头指示眼底周边部出血斑,黄色箭头指示后极部多处黄色硬性渗出;图 1E、图 2E 浅蓝色箭头指示新鲜光凝斑,深蓝色箭头指示陈旧性光凝斑

微血管瘤是视网膜末端毛细血管的局部扩张,眼底彩色照相上表现为类圆形的红色或暗红色斑点,边缘清晰 (图 1A、1B 粉色箭头)。FAF 上可见大小不一的点状弱荧光,位于血管上,对于极其微小的血管瘤,FAF 有助于诊断 (图 2A、2B 粉色箭头)。

出血斑眼底彩色照相显示浅层出血为火焰状,深层出血呈暗红色、卵圆形、斑片状 (图 1C、1D 红色箭头)。FAF 上因出血遮蔽视网膜和脉络膜荧光,表现为自发荧光减弱区,与眼底彩色照相对比,可以增强

视网膜出血,尤其是点片状出血的显影 (图 2C、2D 红色箭头)。

渗出由蛋白或液体自血管中渗出,进入周围组织。眼底彩色照相上硬性渗出呈黄白色,界限清,由色泽的点状融合成片状,呈环形、扇形、星芒形或不规则分布 (图 1D 黄色箭头);棉絮斑呈白色羽毛样或棉絮样,边界不清。FAF 上表现为荧光强度稍增强的区域 (图 2D 黄色箭头),但对比度不如眼底彩色照相好。

视网膜光凝斑眼底彩色照相可见新鲜光凝斑中心为灰白色,周围绕一浅灰色晕(图 1E 浅蓝色箭头)。陈旧性光凝斑颜色加深、光斑变小(图 1B、1E 深蓝色箭头)。FAF 检查示新鲜光凝斑中间圆点状强自发荧光,周围绕以弱自发荧光(图 2E 浅蓝色箭头)。陈旧的光凝斑为模糊不清的弱自发荧光,与斑片状出血类似,易混淆,不如眼底彩色照相显影清晰(图 2B、2E 深蓝色箭头)。

### 3 讨论

目前 DR 的临床诊断主要依赖眼底彩色照相和 FFA,虽然诊断的特异度及灵敏性均较高,但观察范围有限并需散瞳,且 FFA 为侵入性检查,高血压、荧光素钠过敏的患者均不能行该项检查。2000 年欧堡公司推出了超广角眼底彩色照相,能在免散瞳和不接触眼睛的情况下就观察到 82% 的眼底视野,诊断 DR 的灵敏度和特异度高达 76%<sup>[4]</sup>,克服了传统眼底彩色照相存在周边视野盲区的缺陷。FAF 主要来源于眼底 RPE 细胞代谢产物脂褐质,脂褐质的组成成分为 A2E (N-亚视黄基-N-视黄基-乙醇胺),FAF 基于荧光团被特定波长的光激发,并反过来发射特征光谱,可间接反映活体 RPE 细胞及感光细胞代谢状态<sup>[5]</sup>。现已可用于年龄相关性黄斑变性、中心性浆液性脉络膜视网膜病变、脉络膜肿瘤、炎症疾病、遗传性疾病、视网膜脱离等疾病的诊断与随访<sup>[6]</sup>。但还鲜有报道将 FAF 应用于 DR 的诊断中。

正常的眼底彩色照相可以清晰地显示视网膜动静脉、视盘、黄斑中心凹的结构。正常 FAF 上视盘缺乏 RPE 组织,无自发荧光;视网膜血管中的血红蛋白吸收自发荧光,荧光减弱;黄斑区的叶黄素吸收自发荧光,从中心凹向外层荧光逐渐增强;黄斑以外视网膜荧光均匀分布。

本研究比较了 40 例(80 眼)NPDR 患者的超广角眼底彩色照相和 FAF,发现两者的图像质量基本一致,均能反映周边部视网膜的情况。眼底彩色照相的结果是通过绿色或红色单色光照片和二者的混合伪彩色照片形式呈现,更接近于前置镜下看到的眼底图像。FAF 主要通过荧光强弱来判断病变的位置及性质。在各种典型的眼底病变中,微血管瘤、出血斑这两种眼底改变在眼底彩色照相上虽然都有特异性的表现,但是极其微小的血管瘤以及点片状视网膜出血的显影在 FAF 上有增强,有助于细微病变的诊断,尽管两种检查对比差异并无统计学意义(均为  $P > 0.05$ )。渗出在 FAF 上的显影并不明显,分辨率也不够,两种检查的阳性率对比,差异有统计学意义( $P = 0.044$ );黄斑水肿则在 OCT 中可以更为敏感和准确地检出,在以上两种检查中的敏感性相对较差。视网膜新鲜性光凝斑在两种模式检查上均显影清晰,陈旧性光凝斑在 FAF 上易与出血混淆,必须谨慎诊断,眼底彩色照相和 FAF 对比差异有统计学意

义( $P = 0.047$ ),主要是由于陈旧性光凝斑显影的分辨率不够,且因部分与出血难以鉴别,未能正确诊断。尽管 FAF 异常与伪彩色图像上可见的视网膜改变相关性很好,但在某些情况下存在着细微差异,表明 FAF 可给我们提供更多信息<sup>[7]</sup>。

在 DR 中,脂褐素由不同脂质和蛋白质的过氧化产物组成,因此脂褐素被认为是视网膜中氧化过程的标志<sup>[8]</sup>。有研究表明,小鼠的脂褐素的积累在小胶质细胞中可能比在 RPE 中更大<sup>[9]</sup>。目前,DR 的病理生理过程通过激活小胶质细胞,允许氧化副产物的激活和形成,从而形成可通过 FAF 检测到的脂褐素颗粒<sup>[8-9]</sup>。目前,FAF 在 DR 患者诊断中有效性还未有大样本的临床研究。然而,基于动物研究和小型临床研究,FAF 显示出巨大的潜力,并有望成为诊断 DR 患者的重要影像技术<sup>[10]</sup>。

尽管超广角系统的多模式检查有诸多优势,但眼底成像范围的扩大可能会牺牲一部分图像分辨率,且目前该技术尚存在上下方周边部视网膜图像部分损失,患者睫毛、屈光间质病变均容易形成伪影。眼底彩色图像为伪彩色,有后极部图像分辨率较低、需要受检者的配合度较好等缺点。尽管在眼底成像时出现的伪影会部分干扰对检查结果的判断,但是并不影响在眼底周边部病变检查方面所表现出的明显优势<sup>[11]</sup>。目前临床医师并未充分利用这项新技术获得更加丰富的眼底信息,尤其是超广角 FAF,提高其应用水平更亟待思考和探索。

由于是回顾性分析,本研究尚存一些不足。如成像方式和其他临床数据不一定以标准化方式获得(如并非每例患者都具有彩色照相和 FAF 图像)等。因此,为了进行对比分析,必须排除许多病例来使数据集均匀化,从而引入潜在的选择偏倚以及病例数的极大削减,有待今后扩大样本量进一步完善。

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【应用研究】

# 雷珠单抗联合激光光凝术治疗视网膜分支静脉阻塞(BRVO)继发黄斑水肿疗效观察

杨大勇 李琳

作者简介:杨大勇,女,1978年2月出生,内蒙古人,博士,副主任医师。主要研究方向:玻璃体视网膜疾病、白内障。联系电话:13948412307;E-mail: yangdy782@126.com; ORCID:0000-0002-5683-0471

About YANG Da-Yong: Female, born in February, 1978. Medical doctor, associate chief physician. Tel: 13948412307; E-mail: yangdy782@126.com; ORCID: 0000-0002-5683-0471

收稿日期:2018-02-05  
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本文编辑:方红玲  
作者单位:010050 内蒙古自治区呼和浩特市,内蒙古医科大学附属医院眼科  
通讯作者:李琳, E-mail: lilin0627@163.com; ORCID: 0000-0002-1761-3415

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From the Department of Ophthalmology, Affiliated Hospital of Inner Mongolia Medical University, Huhehaote 010050, Inner Mongolia Autonomous Region, China

Responsible author: Li Lin, E-mail: lilin0627@163.com; ORCID: 0000-0002-1761-3415

The eye pressure of B group and C group in 6 and 12 months after treatment were significant better than that of A group ( $F=2.45, 2.60, P=0.03, 0.02$ ). There was no significant difference in the complications incidence among the 3 groups ( $\chi^2=2.14, P=0.38$ ). **Conclusion** Compared with laser photocoagulation and ranibizumab administration alone, the combination methods for the treatment of patients with macular edema secondary to BRVO can achieve efficiently higher visual acuity, reduce the levels of CMT.

**【Key words】** ranibizumab; laser photocoagulation; branch retinal vein occlusion; macular edema; clinical effects; safety

## Ranibizumab combined with laser photocoagulation in the treatment of patients with macular edema secondary to branch retinal vein occlusion

YANG Da-Yong, LI Lin

**【Abstract】 Objective** To investigate the efficacy of laser photocoagulation and ranibizumab for the treatment of patients with macular edema secondary to branch retinal vein occlusion (BRVO). **Methods** Totally 90 patients with macular edema secondary to BRVO were chosen in the period from January 2015 to December 2016 in our hospital and randomly divided into 3 groups including A group (30 patients) undergoing ranibizumab administration alone and B group (30 patients) receiving laser photocoagulation alone and C group (30 patients) receiving both ranibizumab administration with laser photocoagulation; and the levels of the best corrected visual acuity (BCVA) and central macular thickness (CMT) and eye pressure before and after treatment and the complications incidence of the three groups were compared. **Results** The levels of BCVA of A group in 3 months, 6 months and 12 months after treatment were  $0.80 \pm 0.12, 0.72 \pm 0.08, 0.67 \pm 0.06$ , respectively; the levels of BCVA of B group in 3 months, 6 months and 12 months after treatment were  $0.63 \pm 0.09, 0.60 \pm 0.06, 0.47 \pm 0.04$ , respectively; the levels of BCVA of C group in 3 months, 6 months and 12 months after treatment were  $0.59 \pm 0.06, 0.54 \pm 0.05, 0.43 \pm 0.04$ , respectively. The levels of BCVA of B group and C group in 3 months, 6 months and 12 months after treatment were significant better than A group ( $F=2.51, 2.68, 2.91, P=0.03, 0.02, 0.02$ ). The levels of CMT of A group, B group and C group in 3 months, 6 months and 12 months after treatment were  $(359.15 \pm 77.95) \mu\text{m}, (365.27 \pm 53.38) \mu\text{m}, (300.25 \pm 39.01) \mu\text{m}; (304.32 \pm 59.20) \mu\text{m}, (327.68 \pm 40.91) \mu\text{m}, (246.23 \pm 30.04) \mu\text{m}$  and  $(209.30 \pm 54.39) \mu\text{m}, (264.33 \pm 37.80) \mu\text{m}, (208.17 \pm 29.34) \mu\text{m}$ . The levels of CMT of B group and C group in 3 months, 6 months and 12 months after treatment were significant better than those of A group ( $F=3.78, 4.66, 5.14, \text{all } P=0.00, 0.00, 0.00$ ). There was no significant difference in the eye pressure in 3 months after treatment among the 3 groups ( $F=0.95, P=0.64$ ).

The eye pressure of B group and C group in 6 and 12 months after treatment were significant better than that of A group ( $F=2.45, 2.60, P=0.03, 0.02$ ). There was no significant difference in the complications incidence among the 3 groups ( $\chi^2=2.14, P=0.38$ ). **Conclusion** Compared with laser photocoagulation and ranibizumab administration alone, the combination methods for the treatment of patients with macular edema secondary to BRVO can achieve efficiently higher visual acuity, reduce the levels of CMT.

**【Key words】** ranibizumab; laser photocoagulation; branch retinal vein occlusion; macular edema; clinical effects; safety

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