·文献综述·

豹纹状眼底与眼部和全身疾病的相关性及其在人工智能下的识别与量化

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摘要
豹纹状眼底在近视和老年人群中常见,是一种容易被观察和评估的眼底改变。纵向随访观察到豹纹状眼底改变可以保持长期稳定,也可以进一步发展而导致更严重的眼底病变和视觉质量下降。豹纹状眼底的临床重要性不仅是其作为近视性黄斑病变(MMD)发展的早期体征及预测指标,在一定程度上也可以辅助其他眼部及全身疾病如青光眼、糖尿病视网膜病变、年龄相关性黄斑变性、认知功能障碍、唐氏综合征的早期识别及机制研究。目前,人工智能(AI)在豹纹状眼底的识别、分级和量化应用中取得了显著的成果。故文章讨论了豹纹状眼底改变相关的眼部与全身疾病及其潜在机制,以及 AI 对豹纹状眼底的识别和量化进展,以期为后续相关研究有所帮助。
关键词:豹纹状眼底;近视;青光眼;糖尿病视网膜病变;年龄相关性黄斑变性;认知功能障碍;唐氏综合征;人工智能
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Research progress of the correlation between fundus tessellation with ocular and systemic diseases as well as its identification and quantification based on artificial intelligence

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Abstract
• Fundus tessellation, commonly observed in individuals with myopia and among the elderly, represents a fundus alteration easily discernible and assessable. Long-term monitoring has revealed that fundus tessellation may persist unchanged for extended periods or progress, potentially leading to more severe fundus lesions and diminished visual quality. The clinical significance of fundus tessellation is not only as an early indicator and predictor of myopic macular degeneration (MMD), but also, to some extend, as a helpful assistance in early identification and mechanism research of the other ocular and systemic disease, including glaucoma, diabetic retinopathy, age-related macular degeneration, cognitive impairment, and Down syndrome. Currently, artificial intelligence (AI) has achieved remarkable results in detecting, grading, and quantifying fundus tessellation. Therefore, this paper discusses the ocular and systemic diseases related to changes in fundus tessellation, their underlying mechanisms, and advancements in AI-based identification and quantification of fundus tessellation, aiming to contribute to future research endeavors.
• KEYWORDS: fundus tessellation; myopia; glaucoma; diabetic retinopathy; age-related macular degeneration; cognitive impairment; Down syndrome; artificial intelligence

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0 引言

豹纹状眼底定义为在黄斑中心凹及血管弓周围均可以清晰观察到脉络膜血管[1],因似豹纹样纹理而得名。其产生机制尚不明确,现有的研究认为导致脉络膜大血管可见度增加的因素包括视网膜色素上皮层色素减少、视网膜血管密度及厚度下降、眼轴增长及年龄增大所致脉络膜变薄及毛细血管萎缩、脉络膜黑色素细胞密度下降等[2-7]。豹纹状眼底是近视性黄斑病变自然病程中最早期的病变[1],也是脉络膜变薄的临床标志物[4],并且与青光眼、糖尿病视网膜病变(diabetic retinopathy, DR)、年龄相关性黄斑变性(age related macular degeneration, ARMD)、认知功能障碍等眼部及全身疾病具有潜在联系。因此,早期对豹纹状眼底进行识别和筛查对相关疾病预后具有重要意义。

目前,眼底彩色照相简便快捷,应用广泛,通过人工智能(artificial intelligence, AI)对眼底彩照中豹纹状眼底进行识别及量化不仅快速及准确,并且实现了豹纹状眼底的实时监测和病理性近视的及时转诊。现本文就豹纹状眼底与多种眼部和全身疾病的相关性研究,及其在人工智能下识别和量化进展作一综述,以期为相关疾病发病机制的探讨及预后判断提供依据。

1 与豹纹状眼底改变有关的眼部及全身疾病

1.1 眼部疾病

1.1.1 近视 豹纹状眼底是近视的常见特征[8],也是高度近视的标志[9-10]。依据 Ohno-Matsui 等[1]于 2015 年提出的国际近视性黄斑病变(myopic macular degeneration, MMD)分级标准,MMD 被分为无近视性黄斑病变、豹纹状眼底、弥漫性脉络膜视网膜萎缩、斑片状脉络膜视网膜萎缩及黄斑萎缩 5 个等级,其中豹纹状眼底被认为是 MMD 自然病程中最早期的病变。尽管单纯的豹纹状眼底改变不属于病理性近视,但随访研究显示,豹纹状眼底可以长期稳定,也可以进展到 MMD 的晚期阶段,例如弥漫性视网膜脉络膜萎缩,后巩膜葡萄肿,漆裂纹,最后可以进展为脉络膜新生血管和黄斑萎缩[11-15],评估豹纹状眼底将有助于理解病理性近视眼底改变的发病机制[16]。虽然这种进展需要相当长的时间,但超过豹纹状眼底这一阶段后往往进展得更快[12],且与成年人相比,儿童和青少年在出现豹纹状眼底的情况下,MMD 进展的可能性更大[17]。因此,早期辨别豹纹状眼底的严重程度对评估眼底损害的远期进展具有重要意义。纵向研究表明,豹纹状眼底是识别屈光进展高风险儿童的潜在指标[18],也是预测 MMD 发展的主要指标[19]。随着 MMD 的发展,眼轴会逐渐增加,等效球镜度数逐渐减小,最佳矫正视力逐渐恶化,脉络膜逐渐变薄[11],并且,与晚发的眼睛相比,早发豹纹状眼底的眼睛脉络膜更薄[20],豹纹状眼底与脉络膜厚度紧密相关,可以作为脉络膜变薄的临床标志[4]。由此可见,豹纹状眼底的发展与近视进展和视力预后存在密切相关性,需要更多的纵向研究探索其作为近视临床标志物的预测价值。

1.1.2 青光眼 近视是青光眼尤其是正常眼压性青光眼的一个重要危险因素[21]。Jonas 等[5]对原发性开角型青光眼(primary open angle glaucoma, POAG)合并高度近视患者进行了形态学测量与分析,发现豹纹状眼底与 POAG 的发生相关,并且豹纹状眼底亚组年龄更大、眼压更低、视盘旁萎缩更大以及神经视网膜边缘变薄,这与既往研究发现的视盘旁萎缩与更明显的豹纹状眼底、弥漫性神经纤维层丢失和仅中度升高的眼压有关较为一致[22],推断在相对低眼压的老年患者中,POAG 具有独特的亚型,主要导致视神经弥漫性萎缩。一项基于人群研究中发现,豹纹状眼底改变与更大的视盘旁萎缩和更高的青光眼性视神经病变患病率显著相关[4],这证实了 Jonas 等[5]的结论。因此,对于那些伴有明显豹纹状眼底改变的青光眼患者,他们虽然眼内压正常或更低,但由于豹纹状眼底和视盘旁萎缩影响视网膜色素上皮和光感受器[5,23],可能会更容易出现弥漫性视神经萎缩,需要及时干预。并且,视盘周围视网膜神经纤维层(retinal nerve fiber layer, RNFL)和视盘周围视网膜血液供应下降也在豹纹状眼底患者中被检测到[24],由此推测豹纹状眼底可能也会通过影响 RNFL 及视神经的血液供应进而导致近视患者青光眼的发病率上升。此外,在高度近视患者中发现,随着豹纹状眼底等级的增加,会出现颞上方的 RNFL 增厚[25],而 POAG 患者各象限均变薄[26]。因此,如果豹纹状眼底患者出现视盘旁颞上方部位的 RNFL 变薄,应警惕青光眼的发生,豹纹状眼底的改变可能有助于近视患者 POAG 的早期识别。

1.1.3 糖尿病视网膜病变 DR 是糖尿病最常见的严重微血管病变之一,其发生与进展和糖尿病病程、高血压病程、血糖水平、糖化血红蛋白水平及遗传和肥胖等因素密切相关[27]。值得注意的是,在部分患者中,尽管合并 DR 的危险因素,仍没有发生 DR,这表明存在局部因素预防这类血管性眼病。据此,多项临床和流行病学研究结果显示近视是 DR 的保护因素[28-30]。在此基础上,越来越多的报道表明豹纹状眼底与 DR 发生发展负相关[31-34],证实了具有豹纹状眼底的眼更不易发生 DR。根据既往研究推测,豹纹状眼底改变与眼轴伸长密切相关[4],随着后巩膜的伸展及脉络膜视网膜变薄,氧气需求量减少,从而减轻了糖尿病引起的缺氧应激及 DR 风险[35]。其次,豹纹状眼底患者视网膜血流密度降低,动脉灌注压下降[36-37],这阻止了 DR 出现前的异常高灌注状态[32],从而降低了 DR 的风险。再者,豹纹状眼底改变的患者还会出现视网膜色素上皮细胞减少,进而减少了转化生长因子-β 等细胞因子的分泌,使血管内皮细胞生长因子的表达降低[31]。因此,合并豹纹状眼底可能比单纯的长眼轴或屈光不正发生 DR 的风险更低,这有助于临床医生评估糖尿病患者 DR 发病及进展风险。

1.1.4 年龄相关性黄斑变性 ARMD 是发达国家老年人群视力丧失的主要原因[38]。Spaide[39]分析了 17 例年龄相关性脉络膜萎缩(脉络膜厚度<125 μm)患者的 28 眼,发现所有眼睛均表现出豹纹状眼底。Switzer 等[6]在一项针对早期 ARMD 眼的研究中报道了更高的豹纹状眼底程度与更薄的黄斑中心凹下脉络膜厚度之间的相关性。脉络膜厚度变化是 ARMD 发病的关键之一[40-41],从组织学上分析,ARMD 患者脉络膜中小血管丢失,剩余的大血管占据了其余脉络膜的全层[42],故由于脉络膜萎缩伴大血管裸露呈现出豹纹状眼底改变。目前关于 ARMD 与豹纹状眼底的直接相关性尚未得到充分认识,一项以人群为基础的研究发现豹纹状眼底改变的严重程度与中晚期 ARMD 发生率负相关[4],但具体机制尚不清楚,因此豹纹状眼底可能为 ARMD 的发病及进展机制提供线索,但需进一步研究明确。另外,息肉样脉络膜血管病变(PCV)是新生血管型 ARMD 的重要亚类,也是厚脉络膜谱系病之一[43]。2013 年,Warrow 等[44]首次使用厚脉络膜的术语,报道了 9 例脉络膜增厚型色素上皮病变,由于此类患者脉络膜增厚,其眼底检查均可见豹纹状眼底变淡。因此,眼底彩照上豹纹状眼底的减轻或缺失成为了识别厚脉络膜疾病的特征之一[43,45-46]。

1.2 全身疾病

眼与全身多个系统密切相关,眼部症状和体征能够作为部分全身疾病早期识别的生物标志物,进而

来辅助相关疾病的早期诊断及治疗。有学者研究发现较高的豹纹状眼底程度与轻度认知功能障碍相关[47],且有认知功能障碍的人群豹纹状眼底进展得更快[48],豹纹状眼底可能是早期认知功能下降的一个指标,解剖上大脑和脉络膜均由颈内动脉供血的证据可以对此关联作出部分解释。并且,既往研究提示脉络膜变薄可作为阿尔兹海默症(Alzheimer disease's, AD)的早期生物标志物[49-53],依据豹纹状眼底与脉络膜变薄的密切相关性推断,豹纹状眼底有潜力作为早期识别认知功能障碍的临床表现,对于年轻的或者尚未出现临床症状的患者辅助眼底检查,观察到严重的豹纹状眼底可能对早期认知功能障碍的诊断具有提示作用。此外,Postolache 等[54]发现与正常儿童相比,唐氏综合征(Down syndrome, DS)儿童的豹纹状眼底发病率更高。此类群体中高度近视的儿童更多,脉络膜的机械拉伸在一定程度上可以解释这一现象。然而,DS 非高度近视以及远视和散光患儿出现豹纹状眼底表明,与一般近视人群相比,DS 人群的豹纹状眼底病理生理机制有所不同。结合既往研究,DS 患者易患有 AD[55],能观察到与 AD 类似的脑微血管密度降低[56],这提示血管生成失调[57]导致的脉络膜血管稀疏参与了非高度近视眼的豹纹状眼底的发生。深入研究 AD 及 DS 患者血管生成的特殊生理及病理状态,有可能发现适用于预防和治疗眼部新生血管形成的宝贵信息[54]。目前关于豹纹状眼底与全身疾病的研究证据有限且缺乏对其机制的深入探讨,未来需要更多的研究评估豹纹状眼底是否可作为全身性疾病尤其是血管性疾病发生发展的候选生物标志物。

2 豹纹状眼底在人工智能下识别和量化

豹纹状眼底与上述眼部及全身疾病的发生和进展具有密切联系,早期及时地识别豹纹状眼底不仅有助于对相关疾病的诊断,还能更好地判断疾病进展与预后,对临床实践有重要的指导意义。既往研究提出了几种主观的方法[4,14,58-59],但逐渐发现主观地对豹纹状眼底进行识别和分级不仅耗时耗力,也降低了其正确率和可重复性。因此,迫切需要一种客观及快速的评价手段来提高对豹纹状眼底的临床筛查及分级水平。随着 AI 技术的飞速发展,机器学习及深度学习算法和体系在多个学科疾病中展现了出色的性能。就眼科而言,人工智能依赖于眼科图像,尤其是眼底彩色照相在多种眼科疾病(如 DR、ARMD、青光眼性视神经病变、病理性近视等)的自动识别和量化分割任务中取得了成功的应用[60-63]。因此,研究者们利用眼底彩照,构建了多种模型来识别、定位和量化豹纹状眼底。

Xu 等[64]在 2016 年首次提出了一种在计算机辅助下的豹纹状眼底自动检测方法,并证明了机器学习在豹纹状眼底检测上的有效性及可靠性。Pan 等[65]利用 Inception V3 和 ResNet-50 深度学习模型将眼底图像分为了正常、黄斑变性和豹纹状眼底三类,能够迅速准确地在眼底图像中识别出豹纹状眼底。Lyu 等[66]采用了迁移学习技术,结合预训练的 GoogLeNet 构建了高准确率的豹纹状眼底的分类器。此外,研究者们还构建出了双流深度卷积神经网络(DCNN-DS)模型[67]、ResNet50 网络联合 DeepLabV3 + 网络的协同决策模型[68]、基于视觉识别的 VOLO-D2 模型[69],成功实现了深度学习对近视性黄斑病变的分类,并利用特征融合策略[70]、ALFA-Mix+主动学习算法[71]等技术,不断提高模型的分类性能,在近视性黄斑病变分级领域呈现出研究深入化、数据扩大化、算法高效化、模型多样化的发展趋势。

为了进一步达到对豹纹状眼底进行自动分级的目的,熊荔等[72]研发了一种能够基于脉络膜血管,将盘周豹纹状眼底像分为无、轻度、中度和重度四个级别的算法。Wang 等[73]基于医院数据库,利用 EfficientNet-B8 模型构建了一种能够有效检测及分类正常、轻度、严重豹纹状眼底的模型,并且在严重豹纹状眼底的识别性能上优于人工。Ju 等[74]提出使用 CycleGAN 模型利用常规眼底图像来帮助训练欧堡超广角眼底图像(UWF) 数据集,以此进一步实现了在 UWF 图像上豹纹状眼底的分割和分级。另外,Yao 等[75]报道的 DeepGraFT 新方法,能够根据早期糖尿病视网膜病变治疗研究(ETDRS)分级量表,实现豹纹状眼底自动分级,有潜力成为预测病理性近视进展的临床决策支持工具。

近几年,还有一种新的定量方法被提出,它基于 ResnetFCN 模型从眼底图像中提取暴露的脉络膜,然后计算出单位面积眼底的平均暴露脉络膜面积,定义为豹纹斑密度[76]。研究者们通过将豹纹斑密度与手动评级方法结合,计算出不同人群不同等级豹纹状眼底的阈值作为参考值,用于指导豹纹状眼底严重程度的评估和临床眼底病的筛查[77-78]。郭振等[79]还构建出适配近视患者眼底豹纹分割模型,能够结合基于深度卷积神经网络的目标检测模型定位黄斑及视盘周围区域,识别全图及局部区域的豹纹斑密度,更准确地辅助临床预测和评估豹纹状眼底改变对近视进展的影响。

现有的 AI 模型实现了豹纹状眼底的早期识别和量化分析,与手动分割性能相当或更优,并能实时监测其进展,有助于对具有病理性近视风险的人群早期预警和及时转诊。然而,尽管相关研究不断增多,但目前对于豹纹状眼底的远期预测及预后评估尚处于初级探索阶段,将 AI 科学研究成果用于临床诊疗仍面临挑战,需要开展更多真实世界研究以提高临床实践与应用的可行性。

3 总结与展望

综上所述,豹纹状眼底为识别和诊断眼部及全身多种疾病提供了重要的辅助价值,尤其是在近视领域中,豹纹状眼底改变被视为单纯性近视过渡到病理性近视的首个迹象,对预防近视性黄斑病变引起的视力丧失至关重要,需对其进行早期识别及监测。眼底成像技术应用普遍,基于 AI 模型的工具可以定性及定量分析豹纹状眼底密度及萎缩弧面积等,与临床医生合作后,进一步指导全科或非专科医生对近视性黄斑病变的分诊和转诊决策以及眼科医生的诊断及治疗决策。此外,目前已有不少利用 AI 分析不同人群和群体中豹纹状眼底分布特征及影响因素的报告,但由于纵向数据缺乏,导致这些结果的预测价值较低。因此,为了进一步评估豹纹状眼底在预测近视黄斑进展以及其他眼部和全身疾病方面的临床价值,以及为了早

期识别存在近视性黄斑病变进展风险的个体并进行及时的干预,有必要进行更多的纵向研究及长期随访。

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