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· 综述 ·

早产儿屈光状态与眼部生物特征的研究进展

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摘要:早产儿通常比足月儿具有更高的屈光不正发生率,这种情况尤其多见于伴发早产儿视网膜病变(retinopathy of prematurity, ROP)的早产儿。屈光状态与眼部生物学形态密切相关,早产儿角膜、前房和晶状体等眼部结构的形态会发生变化,且部分眼部生物特征改变被认为与其屈光状态密切相关。随着现代围产期医疗水平的提升,早产儿存活率升高,早产及 ROP 所致的屈光不正人群数量也随之增加,其中近视及高度近视的视力损害和远期不良并发症最为严重。因此关注这一群体的长期屈光预后以及保障其远期生活和学习质量则显得尤为重要,本文就近年来关于早产儿屈光状态和眼部生物特征的研究发现进行综述。

关键词:早产儿;早产儿视网膜病变;足月儿;屈光状态;近视;生物特征;角膜曲率
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Research progress on refractive status and ocular biometrics in preterm births

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Abstract: People who were born prematurely, especially those with retinopathy of prematurity (ROP), usually have a higher incidence of refractive errors than those who were born at full term. The refractive status is closely related to the ocular morphology. The morphology of the ocular structures, such as the cornea, anterior chamber, and lens, changes in preterm infants. Additionally, some changes in ocular biometrics were considered to be related to the refractive status. With improvements in modern medical technology, the survival rate of preterm infants has increased, resulting in an increase in the number of people with refractive errors caused by preterm birth and ROP. Among these, the visual impairment and long-term complications caused by myopia are the most serious. Therefore, focusing on the long-term refractive prognosis and ensuring a lengthy quality of both life and learning are urgently required. In this article, we review recent research findings on refractive status and ocular biometrics in preterm births.

Key words: Preterm birth; Retinopathy of prematurity; Full-term birth; Refractive state; Myopia; Biological characteristic; Corneal curvature

早产对视觉发育具有重要影响,既往研究发现[1-6],早产儿发生屈光不正和眼球形态发育异常等眼部并发症的风险较高。据估计,全世界 2014 年早产率为 10.6%,相当于 1 484 万早产儿[7]。其中,发生早产儿视网膜病变(retinopathy of prematurity, ROP)的患儿上述眼部并发症的发生率更高,病变程度更重。ROP 是一种发生在早产儿的周边视网膜血管发育不良和血管增殖性疾病[8],发生率为 12.7%~38%[9-13]。低出生胎龄和低出生体质量是 ROP 的主要风险因素[14]。随着围产技术和新生儿重症监护技术的发展,低出生胎龄和出生体质量的早产儿的存活率不断提高,ROP(尤其是病变 3 期及

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以上需要治疗的严重 ROP）患儿随之增多[15]。在早产及 ROP 所致的屈光不正并发症中，近视及高度近视最受关注，随着全球近视人口不断增加[16]，早产及 ROP 所致的近视人群的增加或是其中一个重要因素。

与屈光状态相关的眼部生物结构包括眼轴、角膜、前房、晶状体，通过了解以上生物特征的变化将有助于明确早产儿屈光并发症的变化发展及其病理机制。本文将以近 5 年发表的文献为主，对早产儿出生后的屈光状态和与以上生物结构相关的特征进行综述，以期对早产儿的屈光预后评估和近视防控政策提供参考。

1 早产儿的眼球发育及其影响因素

与足月（出生胎龄≥37 周）儿相比，早产儿全身的大部分组织器官（包括眼球）处于尚未发育成熟的阶段，也更容易受到外界因素的干扰。患有 ROP 的早产儿眼球发育不仅会因早产而停滞（主要表现为眼前节发育阻滞[17]），还可能受到 ROP 的影响而发生眼球形态的改变。除此之外，眼底成像技术的改进、抗血管内皮生长因子（vascular endothelial growth factor，VEGF）药物的广泛应用、人工智能和远程医疗[18]等新型诊疗技术的兴起，在使大量的 ROP 患儿得到及时诊断和高效治疗的同时[19]，也增加了影响其眼球发育的风险因素。接受过治疗的 ROP 患儿更倾向于出现屈光不正和眼部生物特征改变，表明治疗可能进一步影响了 ROP 患儿的眼球发育。

对于早产儿的异常屈光状态和眼球生物特征改变的机制，除了前节停滞理论，其他的解释包括：①早产后的宫外温度低于母体环境中的宫内温度[20]，导致角膜发育迟缓，因此早产儿角膜扁平度低于足月儿，产生屈光不正。②骨质疏松、光感知、视觉剥夺和视网膜功能异常的改变，或产后视网膜病变的发生和治疗[21]导致了眼球的异常发育。③神经外胚层发育的改变[22]。屈光发育与眼部生物特征密切相关，早产、ROP、治疗等因素共同影响了眼球的正常发育并改变其生物形态，导致了屈光不正的眼部并发症，包括近视、远视、散光和屈光参差[23-25]。

2 近视与眼部生物特征

早产儿的屈光不正以较高的近视率和近视程度为主要特征。早在 40 余年前，Fledelius[26]发现早产儿比足月儿更易患近视，且这种倾向持续到成年。其后续研究证实与足月儿相比，早产儿眼球形态发育异常（即眼前节发育受抑制），表现为角膜曲率半径较小、晶状体较厚以及眼轴较短，但未发现这些特征改变与近视有明显相关性[17,27]。由于有和无 ROP 的早产儿在屈光状态和生物特征上具有明显差异，故对二者分别进行阐述。

2.1 无 ROP 的早产儿

与足月儿相比，无 ROP 早产儿更容易发生近视和高度近视[3,28-32]。无 ROP 早产儿在儿童期[4,28,31-36]和成年期[3,37-38]都具有相似的眼球生物特征改变，与足月儿相比，早产儿角膜曲率变陡、角膜直径变小、前房深度变浅、晶状体变厚以及眼轴长度变短等。这种特征与眼前节发育阻滞[17]表现类似，其中增加的眼轴长度和变陡的角膜曲率被认为与早产儿近视的发生发展密切相关[3,37]。有研究用低出生体质量儿代替早产儿（出生体质量与出生胎龄密切相关，低出生体质量被认为是早产的代表[39-40]），同样发现，与足月儿相比，低出生体质量儿的近视程度更高且具有角膜形态更陡峭、角膜直径更小等的眼球形态改变[4,40-47]。然而，早产儿与足月儿的屈光不正和生物特征差异会在儿童期（8～10 岁）逐渐缩小并趋于稳定[3,23,28,48]。有研究证实[24]无 ROP 早产儿与足月儿之间近视率和近视程度的差异在成年期并不明显。

2.2 ROP 患儿

约 10% 的 ROP 患儿需要接受 ROP 治疗[15]。ROP 的主要治疗方式包括视网膜冷冻治疗、视网膜激光光凝治疗、玻璃体腔注射抗 VEGF 药物，而对于发生视网膜脱离的患儿则需行玻璃体切除术等。现普遍认为，玻璃体腔注射抗 VEGF 药物治疗后 ROP 患者发生屈光不正的风险增加[49-50]，但低于激光治疗[51-55]，激光治疗后患儿屈光不正的发展则明显低于冷冻治疗[24]。

早产儿的等效球镜（spherical equivalent，SE）与出生体质量和出生胎龄、ROP 的发生和治疗显著相关[3-4,23-24,31,50,56-57]。一项来自瑞典的研究发现，出生胎龄小于 24 周的 355 例早产儿中，ROP 的患病率高达 92.5%，47.0% 的患儿接受了 ROP 治疗，总体的屈光不正率为 51.0%[23]，明显高于相近年龄段的正常人群[58-59]。研究发现[3-4,5,28,31-32,50,56,60-62]，ROP 患儿（尤其是严重 ROP）近视程度高于无（或轻度）ROP 早产儿和足月儿，治疗过的 ROP 患儿近视程度则明显高于未治疗的 ROP 患儿[3-4,24,28,32,50,56,60-63]。

也有研究认为，未接受过治疗的 ROP 患儿的近视度数与无 ROP 早产儿和足月儿相比无明显差

异[24,30]。存在这些矛盾性证据的可能原因如下：①各研究间对近视的定义差异较大(这些定义中近视的最低度数包括 1.0 m^{-1}、2.0 m^{-1}和 3.0 m^{-1}等)。②研究的组间样本量不均衡，使研究间出现不同的统计学结果。③各研究所针对的研究对象年龄段不同，可能造成研究结果的差异。

在生物特征方面，ROP 患儿(尤其是接受过各类 ROP 治疗)多表现为较陡的角膜曲率、较小的角膜直径、较浅的前房、较厚的晶状体以及较短的眼轴[4,31-32,38,56,60,63-64]。与无 ROP 早产儿相似，ROP 患儿呈现发育停滞的眼球形态。二者最大的差别在于，ROP 患者发生眼部生物特征改变的程度更大[37]。

3 远视与眼部生物特征

目前对于早产儿是否存在异常的远视并发症尚存在争议。有研究结果显示[30-31,47]，与足月儿相比，早产儿或 ROP 患儿(包括治疗后的 ROP 患儿)远视的程度和发生率更高[3,28]。也有研究认为早产儿与足月儿之间的远视没有明显差异。

Mao 等[60]和 Tolia 等[65]对早产儿进行了出生后 1~2 年的眼部随访，Chapron 等[66]在早产儿 5 岁时进行了屈光检查，以上研究均发现远视是早产儿最常见的屈光不正。得出上述结论可能的原因是：① 纳入了具有生理学远视度数的早产儿。众所周知，幼儿期及儿童早期的正常屈光状态即表现为不同程度的远视，此为生理性的“远视储备”。这些研究的对象大部分是处于婴幼儿期或儿童早期的早产儿，故不能排除纳入了远视度数尚在正常范围的早产儿。② 将早产儿近视并发症误归为远视并发症，导致近视人数减少而远视人数增加。这是因为，当具有生理学远视的早产儿出现近视的并发症时，仅表现出近视的趋势，即正视化过程加快，其结局在早期仍为远视。因此，判定早产儿是否有异常的远视，需建立在与基线资料一致的足月儿的正常远视度数进行对比的基础上，并且需要足够多的样本量以提高研究结果的可靠性，而这样的研究较缺乏。因此，不应将研究中出现的远视都归为早产儿屈光不正的并发症之一，尚需观察和收集更多的研究证据做进一步的深入分析。

4 散光与眼部生物特征

与足月儿相比，早产儿(尤其是 ROP 患儿和治疗后的 ROP 患儿)发生散光的风险更高[3-4,23,30-32,46]，且早产儿散光的程度随出生胎龄的降低和 ROP 严重程度的增加而增大[1,4,24,28,31]，并与新生儿期的 ROP 治疗如视网膜激光光凝治疗[28,56]、冷冻治疗[3]等呈正相关。

无 ROP 早产儿是否比足月儿更具有散光易感性尚存争议。有研究认为[3-4,28,31,49]，与足月儿相比，无 ROP 早产儿更易于发生散光。也有部分研究认为[24,47,61]，二者之间的散光程度无明显差异。而对于 ROP 患儿(尤其是接受过治疗的 ROP 患儿)，大部分研究的结果则更趋于一致，认为与足月儿和无 ROP 早产儿相比，ROP 患儿更容易发生散光[3-4,23-24,31-32,49,56,61]。这可能与 ROP 患者接受了治疗有关，治疗使 ROP 患儿的眼球形态发生变化，尤其是角膜形态的改变对散光作用最大。

在早产儿众多的眼部生物特征改变中，角膜和晶状体的形态改变被认为与患有或未患有 ROP 的早产儿的散光发生有较高的相关性，角膜曲率的增加被认为是造成散光的重要因素[31,67]。

5 屈光参差与眼部生物特征

屈光参差通常指同一个体的双眼 SE 差值>1.0 m^{-1}的屈光状态，即双眼球镜相差≥1.5 m^{-1}，柱镜相差≥1.0 m^{-1}。屈光参差病因及发病机制目前尚不明确，可能与遗传、发育、外伤等多种因素有关。发育和 ROP 在早产儿屈光参差的形成中具有不可忽视的作用。

早产儿比足月儿更容易发生屈光参差[3,68-69]。出生胎龄越早，成年期的屈光参差程度越大，这在接受过 ROP 治疗的患儿中表现得更明显[24]，尤其是接受过冷冻治疗的患者[3,45]。除此之外，屈光参差与 ROP 严重程度亦密切相关，可随 ROP 分期的增加而增加[1,24]。

与足月儿相比，无 ROP 早产儿的屈光参差程度和患病率显著增加[3,24]，ROP 患儿的屈光参差程度相比也显著增高[3,68]。而其中，接受过治疗的 ROP 患儿的屈光参差程度高于无 ROP 早产儿和未接受过治疗的 ROP 患儿[3,24]。

因此，我们认为早产儿的屈光参差与其双眼病变程度不等有重要相关性，这种相关性在 ROP 患儿中更加显著。此外，由于 ROP 治疗(如视网膜激光光凝、视网膜冷冻治疗等)很难控制对双眼影响的一致性，或使其成为 ROP 患儿屈光参差的可能原因之一。关于早产儿屈光参差的针对性研究较少，Pétursdóttir 等[3]报道早产儿的屈光参差程度增加与其前房深度变浅有明显相关性。早产儿屈光参差方面的评估和分析需要在未来做更多更深入的分析。

6 展 望

与足月儿不同,早产儿更易于发生屈光不正(尤其是近视和高度近视)及眼部生物特征改变(如角膜曲率变陡、角膜直径减小、角膜厚度增加、前房深度变浅、晶状体增厚和眼轴增长短于预期等)。针对此研究热点,本文通过近几年的最新研究将早产儿的屈光发育和眼部生物特征及二者的相关性进行了总结。此举有助于对早产儿的屈光预后进行评估,从而协助其眼部情况随访。通过认识早产儿屈光改变的病理机制,有助于临床寻找针对性的干预措施以改善不良预后、改进现有的医学诊疗技术,从而提高早产儿的远期生活质量。

然而,目前对早产儿的屈光状态及眼部发育的认识还存在不足,早产儿的远视储备变化情况和远期的远视状态尚存争议。除此之外,我们对于早产儿长期屈光发育变化过程的认识欠连续,对于如何避免和减轻早产儿屈光方面的不良预后和相关并发症也还没有统一和确切的措施。近几年,早产儿屈光状态及眼部发育相关文献的发表量呈增长趋势,未来研究将继续深入进行。

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