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早产儿脑损伤的影响因素研究进展

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摘　要

早产儿脑损伤(BIPI)是早产儿主要的并发症之一。尽管随着诊疗水平和围产期护理提高，早产儿存活率明显上升，但BIPI存活者多遗留神经系统后遗症，包括脑瘫、视力、听力及学习障碍等问题。如何避免BIPI的发生和加重、提高远期生存质量成了围产医学和新生儿科工作者关注的重点。本文将BIPI的一些影响因素如缺血缺氧(HI)、高氧、围产期感染、高低碳酸血症、机械通气、糖皮质激素的使用等相关机制作以下综述，为临床围产医学、新生儿科医生治疗和研究BIPI提供参考和思路。

关键词

早产儿脑损伤，缺血缺氧，感染，机械通气，影响因素

Research Progress on Influencing Factors of Brain Injury in Premature Infants

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Abstract

Objective Brain injury in premature infants (BIPI) is one of the major complications of premature infants. Although the survival rate of premature infants has improved significantly with the improvement of diagnosis, treatment and perinatal care, BIPI survivors are often left with neurological sequelae, including cerebral palsy, vision, hearing and learning disabilities. How to avoid the occurrence and aggravation of BIPI and improve the long-term quality of life has become the focus

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of perinatal medicine and neonatology workers. In this paper, some influencing factors of BIPI, such as ischemia-hypoxia (HI), hyperoxia, perinatal infection, hypercapnia, hypocapnia, mechanical ventilation and the use of glucocorticoids are reviewed as follows, in order to provide reference and ideas for clinical perinatal medicine, neonatologist treatment and research on BIPI.

Keywords

Brain Injury in Premature Infants, Ischemia and Hypoxia, Infection, Mechanical Ventilation, Influencing Factors

1. 引言

早产儿是指胎龄(gestational age, GA) ≤ 37 周(259 天)的新生儿。由于早产儿，特别是极早产儿和超早产儿的解剖学和生理学特点，早产儿脑损伤(brain injury in premature infant, BIPI)的发病率占所有新生儿疾病的 15%，是早产儿主要的并发症之一。随着诊疗水平和围产期护理提高，早产儿存活率明显上升。但存活者中多遗留神经系统后遗症，包括脑瘫、视力、听力及学习障碍等问题[1]。如何避免 BIPI 的发生和加重、提高远期生存质量成了围产医学和新生儿科工作者关注的重点。本文将 BIPI 的一些影响因素如缺血缺氧(hypoxia-ischemia, HI)、高氧、围产期感染、高低碳酸血症、机械通气、糖皮质激素的使用等及相关机制作以下综述，以期望为临床围产医学、新生儿科医生治疗和研究 BIPI 提供参考和思路。

2. BIPI 的发病基础

2.1. 脑发育特点

胎儿的脑发育是一个完整连续过程，从外胚层形成神经管，到神经细胞生发、迁移、定位，直至出生，在任何一个环节上受到损害，都会对以后的神经发育带来影响。在妊娠晚期，大脑的生长非常迅速，皮质表面积增加，折叠变得更复杂。早产的发生极大地干扰了神经发育，其中最重要地是影响了少突胶质细胞(oligodendrocyte, OL)生成和髓鞘的成熟。髓鞘是围绕在轴突外的多层神经胶质膜，由前髓鞘少突胶质细胞(premyelinating oligodendrocytes, pre-OLs)转化为 OL，OL 再增殖分化形成。髓鞘能实现动作电位的跳跃和快速传导，以及加强生命后期的学习和记忆。当妊娠 23~32 周时，pre-OLs 的发育占主导地位，对外界化学及物理变化十分敏感而易受到损伤[2] [3]。

2.2. 病理类型及相关发病机制

BIPI 临床上以脑室周围白质软化(periventricular leukomalacia, PVL)和脑室周围－脑室内出血(periventricular-intraventricular hemorrhage, PIVH)两种病理损伤最为常见[4]。白质损伤的机制主要是围产期炎症和 HI 等引起谷氨酸兴奋毒性和氧化应激，最终导致 OL 成熟停滞、髓鞘形成缺陷。与晚 pre-OLs 的选择性脆弱性、OL 谱系对氧化应激和 HI 的成熟依赖性脆弱性有关[3]。脑室内出血(intraventricular hemorrhage, IVH)主要由于 ① 解剖上早产儿脑室周围室管膜下毛细血管丰富，血管内膜无完整基膜，管壁较薄，脆性高，基底层缺乏纤维连接蛋白和胶原蛋白。② 脑本身的循环调节机制不成熟，一旦遇到外部或内部环境变化(如 HI、外力作用)导致血压快速波动，血管易破裂出血。出血后，炎症及脑损伤可继

续导致 PVL 或弥漫性白质损伤。涉及的机制包括血液释放出大量的血红蛋白、游离铁和其他神经毒性物质，穿过血脑屏障并引发炎症和自由基产生，大脑被免疫细胞浸润，导致神经元和神经胶质细胞凋亡，破坏 OL 的成熟[1]。

3. BIPI 的影响因素

3.1. 缺血缺氧(HI)

产前、产时或产后不久的 HI 都会导致 BIPI [5]。部分早产儿产前暴露于慢性缺氧，如宫内生长受限(intrauterine growth restriction, IUGR)/小于胎龄儿(small for gestational age, SGA)，其定义为出生体重低于同胎龄平均出生体重的第 10 个百分位。IUGR/SGA 是多因素造成的，主要与胎盘功能不全有关。胎儿可利用的 O_2 和营养物质减少，阻碍其高代谢和肌肉组织的生长[6]，通过减缓其生长速度和重新分配心输出量，以有利于大脑、心脏对慢性缺氧作出反应。这种分配方式导致胎儿生长不对称，大脑的正常发育得不到保证。且出生时适应严重反复缺氧的能力降低，对 HI 的易感性增加[5]。

产时或产后不久急性缺氧造成脑细胞无氧代谢增加，乳酸生产增加、ATP 合成减少，钠泵无法工作，胞内钠和钙的积累造成细胞毒性水肿。谷氨酸从胞内释放，激活 pre-OL 和神经元的受体，导致活性氧(reactive oxygen species, ROS)和活性氮(reactive nitrogen species, RNS)产生氧化应激，对细胞结构造成有害修饰(例如脂质过氧化、蛋白质羰基化、DNA 氧化)，从而改变其功能并导致细胞损伤。再灌注的二次损伤形成持续的谷氨酸兴奋毒性，大脑中的炎症反应、ROS 合成、线粒体功能障碍，最终导致细胞死亡[7]。特别是低 GA 早产儿抗氧化酶系统的不成熟对氧化应激的负担增加。在还未形成再灌注伤的缺氧发生后 6 小时内，被认为是可逆转脑损伤的最佳时机。目前较推崇低温治疗、促红细胞生成素和产前硫酸镁的使用[8]。虽然对足月儿缺血缺氧性脑病时使用低温疗法的收益给予肯定，但在 SGA 中使用低温疗法的获益及安全性仍存在争议[9] [10]，Herrera [9]等对接受全身低温治疗的小于 36 周伴 HI 早产儿进行回顾，治疗期间 50%患儿并发凝血障碍、38%并发颅内出血，并且婴儿死亡和远期中、重度神经发育障碍(neurodevelopmental disorder, NDI)发生率很高。在极低早产儿 HI 时使用低温疗法的疗效研究也极少。其他疗法诸如褪黑激素、别嘌醇、N-乙酰半胱氨酸[8]等药物以及动物模型中予以脐带血单核细胞[11]、光生物疗法[12]等在细胞及分子水平抗氧化应激的方法需要更多验证。在这个黄金 6 小时治疗关键窗口期，寻求的是一个具有神经再生特性和强大安全性的神经保护策略，来帮助减轻脑损伤的负担。

3.2. 高氧

与生理性宫内条件相比(pO_2 = 25 mmHg)，早产儿出生后暴露在相对高氧(pO_2 = 75 mmHg)的环境。对于肺不成熟的早产儿，最常见的治疗方法是使用补充氧气和/或机械通气，这加重了高氧效应。研究表明，新生儿期吸入大量氧气会干扰大脑成熟，其机制可能与诱导脑的氧化应激和炎症反应、影响脑血管形成和结构重塑，与髓鞘形成缺乏有关[13]。无论短暂或长期高氧都能增加炎症反应造成 OL 死亡，导致白质发育受损。目前对高氧产生肺损伤的机制研究较多，但对高氧造成脑损伤在细胞及分子水平的研究正在探索阶段，多数基于动物实验。有研究表明促红细胞生成素的重复治疗[14]等将会对因高氧造成的早产儿脑损伤神经发育有益。整体来看，HI 和高氧都会造成 BIPI，但目前来说在早产儿中寻找缺氧和高氧的平衡点仍比较困难的，因为对于危重的早产儿仍需给予氧疗增加存活率。积极对抗氧化应激及管理炎症免疫反应可能是限制 BIPI 的最为有效方法[15]。

3.3. 围产期感染

绒毛膜羊膜炎是早产儿胎盘中最常见的病理异常，其发病率随着 GA 的降低而增加[16]。虽然也有无

感染性炎症，但其发病机制主要是通过妊娠期下生殖道上行感染，其中解脲支原体感染最为常见。侵入性操作、早产胎膜早破和分娩持续时间较长等情况都加大了微生物侵入的概率。即使胎膜完整，但伴有宫颈机能不全、双胎妊娠、胎粪污染羊水等都会增加羊膜腔内感染的风险。严重的绒毛膜炎症反应造成胎盘 HI，应激后使促炎症细胞因子如 IL-6、IL-1α、IL-1β、IL-17A 和 TNFα [17]等的产生和释放，激活母－胎盘－胎儿轴诱发胎儿炎症反应综合征(fetal inflammatory response syndrome, FIRS)，其作用 ① 直接损伤大脑发育。炎症细胞和分子直接损伤 OL 和神经元，并激活小胶质细胞致 pre-OL 进一步损伤，破坏血脑屏障的完整性[18]；② 对额外的围产期或产后伤害的敏感性加强，导致进一步的脑损伤[19]；③ 引发后续发育中的免疫系统和中枢神经系统的持续损伤，甚至影响整个生命周期[20]。但继发于绒毛膜羊膜炎的外周免疫和神经炎症改变的范围和机制目前尚不清楚。

出生后坏死性结肠炎(NEC)早产儿发生 IVH 和/或 PVL 的风险比单独早产高[21]，一项 meta 分析得出，NEC 幸存者中 NDI 的发生率是 40%，严重程度与肠道损伤的程度呈正相关，尤其是在 SGA 中[22]。NEC 的发生通常与早产和低出生体重、肠道和免疫系统发育不成熟、肠道不适当的微生物定植和配方奶喂养有关。但继发性脑损伤的机制目前尚不清楚，可能与 HI、感染和炎症激活肠脑轴，免疫和神经通路影响大脑发育有关。多项研究发现 NEC 动物模型中炎性细胞因子水平升高和血脑屏障破坏，导致区域特异性神经元变性；激活肠 TLR4 信号通路导致肠内高迁移率组 Box1 蛋白释放，激活脑小胶质细胞，引起神经功能障碍[21]。采取有效措施预防 NEC 的发生是近几年的研究热点。目前母乳喂养被确定为对婴儿肠道微生物有益，能预防 NEC 发生；其它如益生菌、益生元、牛乳中的糖胺聚糖的作用效果还需进一步研究[23] [24]。

对于围产期的感染，未来的治疗方向旨在通过控制炎症、抑制小胶质细胞活化和促进未成熟 OL 再生等干预措施来减少脑损伤。临床已经运用的促红细胞生成素，能够减少炎症反应，通过抗氧化酶实现抗氧化作用[25]。另外间充干细胞移植能够在 BIPI 区域释放细胞因子并促进诱导神经干细胞形成、迁移和分化，显著减少了星形胶质细胞增生[26]。脐带血干细胞和脐带衍生细胞治疗能降低促炎细胞因子反应，减少 OL 活化和神经元凋亡[27]。在动物模型中也发现对母体使用黄体酮[28]等药物能减少因炎症引起的胎儿脑损伤。这些发现对后续的临床干预有重要的积极意义。

3.4. 高、低碳酸血症与机械通气

早产儿伴高、低碳酸血症是中枢神经系统损伤的危险因素，可能表现为 IVH、PVL、认知发育障碍和听觉障碍[29]。相关机制有：① CO_2 的波动导致脑血管的变化[30]。脑血管系统对循环气体的水平高度敏感，升高的 CO_2 扩张脑动脉和小动脉促进脑血流量的增加。反之，低碳酸血症致血管收缩和血流减少。② 代谢性酸中毒[31] [32]。PCO_2 变化使 pH 值降低致血管平滑肌松弛，血压变化引起脑血管系统变化。高、低碳酸血症都能在早产儿脑中造成不良结局，因此确定早产儿 CO_2 的标准化范围至关重要。临床上广泛使用机械通气(包括有创通气和无创通气)作为窒息早产儿治疗的必要辅助手段，改善患儿通气障碍，帮助患儿建立自主呼吸。但是机械通气一方面造成高氧暴露、高低碳酸血症，另一方面产生累积压力阻碍了早产儿血液的静脉回流、降低心输出量、阻碍了气道分泌物的清除，使脑血流动力学发生改变，增加 BIPI 发生风险[33]。因此合理设置呼吸机参数也十分重要。综合考虑后，在早产儿中使用较低的潮气量，这种温和的通气方法可降低早产儿辅助通气的不利影响，可能改善存活率和神经系统损伤。允许性高碳酸血症(pCO_2 = 45~54 mmHg [29])是一种允许相对较高水平 CO_2 的通气策略。肺泡内较高的 CO_2 可能会增加 CO_2 的消除刺激新生儿的呼吸驱动，有助于从机械通气中脱机[29]。研究推算出早产儿 pCO_2 的安全范围为 37.5~52.5 mmHg [34]，且极早产和极低出生体重儿可能会受益于允许性高碳酸血症，因为暂时没有发现它会增加 IVH 的发生率[35]。

3.5. 糖皮质激素的使用

产前糖皮质激素(antenatal corticosteroids, ACS)常用于有早产风险的孕妇[36]，加速胎儿器官成熟的作用(尤其是肺部)，减少早产儿的死亡、呼吸窘迫综合征(respiratory distress syndrome, RDS)发生[37]。ACS的短期益处是公认的，但是对BIPI的影响一直存在争议。部分研究表明，ACS能明显减少早产儿白质损伤[38]和IVH [39]发生率。而另外一些研究认为外源性糖皮质激素的使用可能对SGA是有害的[40]。Blankenship [41]发现产前糖皮质激素(antenatal corticosteroids, ACS)可降低SGA的死亡率，但对早产儿IVH和/或PVL发病率没有明显影响。其原因可能是，SGA婴儿最初就暴露于更高水平的内源性皮质类固醇。机制包括增加自身肾上腺皮质醇的产生，降低通过血脑屏障或胎盘去除皮质类固醇的能力，以及阻止母体皮质醇通过胎盘[42]。由于已经暴露于更高水平的内源性类固醇，在即将早产之前额外给予外源性ACS可能不会提供额外的益处。

已发现产后早期使用高剂量的糖皮质激素[43]与脑瘫和NDI的发病率增加有关。在动物模型中也发现，早产窒息后使用糖皮质激素使海马和基底神经节中重要的神经元丢失以及脑室周围白质中全部未成熟/成熟OL的丢失，还可造成高血糖使白质的弥漫性损伤转化为囊性损伤[44]。尽管产后糖皮质激素给药与明显的不良后果有关，在极端早产情况下，低剂量产后给药仍可改善结果，特别是对于依赖呼吸机的早产儿仍建议产后使用糖皮质激素[45]。

不同糖皮质激素的种类的使用似乎对脑损伤产生的影响并不相同[46]，因为目前发现不同种类糖皮质激素对早产儿肺病发展的不同影响[47]，对BIPI的影响是否存在不同需要进一步的临床试验、药代动力学、药效学研究来评估。

3.6. 母亲及其他因素

妊娠合并糖尿病会通过胎盘刺激胎儿内源性产生胰岛素和胰岛素样生长因子1，导致胎儿过度生长，出生后低血糖风险增加[48]。常有合并RDS、NEC、新生儿败血症等并发症[49]被广泛的认为是BIPI的危险因素。妊娠期高血压疾病致BIPI的原因与IUGR有关[50] [51]。妊娠期前体重指数较大的孕妇，对胎儿智力发育有不良影响，可能与DNA甲基化改变有关[52]。整体看来，对妊娠期母亲的健康管理显得至关重要。监测血糖血压水平、饮食营养调整、生活方式改变和体重管理是必不可少的。70%~85%妊娠糖尿病患者可以通过充分的体力活动以及饮食和生活方式的改变血糖水平；优选低血糖指数的高质量复合碳水化合物，有助于减少对胰岛素抵抗[53]。除了常规使用硫酸镁预防子痫外，最新研究表明可用低剂量阿司匹林可预防高危女性的先兆子痫[54]。

阴道分娩极早产儿似乎更容易出现IVH [55]。几项回顾性研究认为，剖宫产可以降低 < 32周早产儿的PIVH风险[56]。其原因可能是产道对早产儿还未发育完全的大脑挤压导致。但目前没有足够的证据证明剖宫产可以降低BIPI的发生率[57]。围产医务人员应该根据孕妇具体情况合理选择分娩方式，以避免其他不良结局发生。

随着延迟生育的女性及有生育问题的人群越来越多，辅助生殖技术已经成为普遍受孕方式之一[58]。研究表明由于体外受精(*in vitro* fertilization, IVF)婴儿早产率较高和出生体重较低，发生脑损伤的风险也增加[59]，但目前仍缺乏更多的证据参考。值得注意的是，似乎男性胎儿[55] BIPI发生率较女性胎儿更高，因此父母可能需要在男性婴儿智力发育中给予更多关注。还有其他一些方法如对有先兆早产的使用缩宫素、延迟脐带钳夹、轻柔复苏可能会减少BIPI的发生[36] [60]。

4. 总结与展望

围产期各种因素单独或联合作用都会导致BIPI，其机制复杂，一部分为明确的危险因素，但仍有一

部分存在较大争议。且关于 BIPI 的发生、发展机制我们还知之甚少，需要进行大量的流行病调查及动物实验以提供充足的证据，来避免 BIPI 以及对临床诊疗工作有更好的指导意义。目前看来，制定个体化的诊疗、实时关注早产儿各项数据变化十分重要。做好孕检，预防妊娠期疾病及孕期管理、避免早产，同时维持早产患儿内环境稳定、避免缺血缺氧、治疗感染、积极有效抗炎、临床轻柔操作等对减轻 BIPI、改善神经系统远期预后具有不容忽视的意义。

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