

新生儿缺氧缺血性脑病的早期监测及预后评估研究进展

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摘 要

新生儿缺氧缺血性脑病(hypoxic-ischemic encephalopathy, HIE)是导致新生儿远期神经功能障碍的重要原因, 其遗留的认知缺陷、运动障碍等后遗症对患儿生活质量及家庭社会负担造成深远影响。近年来, 围产期监护技术显著提升了HIE的早期识别能力, 为判断助产及剖宫产时机及启动神经保护干预争取了关键时间窗。在预后评估领域, 多模态监测策略结合深度学习驱动的影像组学技术, 可有效预测神经发育结局, 进而指导个体化康复方案。本文综述了HIE早期监测与预后评估领域的技术进展, 探讨了人工智能算法整合多模态监测数据的未来应用。

关键词

缺氧缺血性脑病, 脑电图, 磁共振成像, 神经发育结局

Advances in Early Monitoring and Prognostic Evaluation of Neonatal Hypoxic-Ischemic Encephalopathy

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Abstract

Hypoxic-ischemic encephalopathy (HIE) is an important cause of neonatal long-term neurological dysfunction, and its sequelae such as cognitive deficits and dyskinesia have a profound impact on children's quality of life and family social burden. In recent years, perinatal monitoring technology has significantly improved the early identification ability of HIE, and has won a key time window for judging the timing of midwifery and cesarean section and starting neuroprotective intervention. In the field of prognosis evaluation, multimodal monitoring strategy combined with deep learning-driven imaging technology can effectively predict the outcome of neurological development, and then guide individualized rehabilitation programs. This paper summarizes the technical progress in the field of early monitoring and prognosis evaluation of HIE, and discusses the future application of artificial intelligence algorithm to integrate multimodal monitoring data.

Keywords

Hypoxic-Ischemic Encephalopathy, Electroencephalogram, Magnetic Resonance Imaging, Neurodevelopmental Outcome

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1. 引言

新生儿窒息(neonatal asphyxia)是由于宫内窘迫或分娩过程中胎儿呼吸与循环障碍,导致患儿生后无法迅速建立、维持正常呼吸,从而引起缺氧和酸中毒,甚至发生多器官系统功能损伤。由于脑细胞对缺氧敏感,易发生缺氧性损伤,严重者可遗留脑瘫、癫痫等后遗症。新法复苏等先进的围产医学技术推广和围产期保健网络的不断完善,使我国新生儿窒息发病率和死亡率显著下降[1],但窒息相关新生儿脑损伤遗留的神经系统后遗症负担仍有增加趋势[2]。因此,新生儿缺氧缺血性脑病(hypoxic-ischemic encephalopathy, HIE)的早期监测及预后评估值得关注。

本文对 HIE 的早期监测及预后评估研究进展进行综述,旨在总结目前早期监测及预后评估的有效方法及研究前沿,以改善患儿预后、减少新生儿窒息带来的疾病负担。

2. 早期监测

分娩期间的监测有助于产科医生判断助产及剖宫产时机,有助于 HIE 等窒息相关损伤的预防。产时胎心监护(cardiotocography, CTG)已应用约 30 年,现有研究表明连续胎心监护(continuous cardiotocography)较间断听诊能显著降低新生儿惊厥发生率[3]。经验丰富的临床医师可通过产前 1 小时胎心监护,发现约 75%无急性围产期事件而生后发生缺氧相关中重度新生儿脑病的患儿[4]。目前,国内外指南建议采用三级系统评价产前胎心监测,随着类别增加, HIE 发生率显著增加[5] [6]。由人视觉评估 CTG 结果具有主观性,且单独通过 CTG 推断无法兼顾到胎儿个体化代偿能力、羊水是否粪染及宫内感染与否等多个临床因素间的相互作用[7]。通过机器学习模型、计算机化分析等方法,将胎心监测数据与孕母临床数据等结合分析,可进一步提高预测判断准确度,能有效预测胎儿宫内窘迫、有效预警,降低 HIE 患病率[8] [9]。近年来,计算机化 CTG 分析系统效能有所提高,然而胎心监护只起到筛查和提示作用,最终分娩过程中

的处理及时效仍取决于临床工作者。

脐带血为患儿生后易早期获得的标本, 现有研究对脐带血进行代谢组学分析, 结果表明, Apgar 评分结合脐带血乳酸及丙氨酸水平能更有效预测 HIE 发生[10]。HIE 患儿脐带血中缺血修饰白蛋白(Ischemia Modified Albumin, IMA)显著高于对照组, 且随 HIE 严重程度加重而升高[11]。重度 HIE 组患儿脐带血的 Fzd4 mRNA 表达水平显著高于轻中度 HIE 组, 长期神经发育结局重度异常患儿脐带血的 Nfat5 mRNA 表达水平与其余组别间有显著差异[12]。然而, 上述脐带血成分分析研究样本量不大, 临床实用价值及推广均有一定局限性。

3. 预后评估

诊断 HIE 后, 可通过生后 72 小时内神经系统表现的动态评估, 进行临床分度。目前, 临床上主要运用 Sarnat 评分, 部分研究则使用 Thompson 评分等工具。研究表明, 临床分度与患儿头颅磁共振(MRI)呈现的脑损伤类型及其远期神经发育结局密切相关: 分度越重, 患儿发生运动功能障碍、认知缺陷等神经发育异常的风险显著增高。目前临床对 HIE 预后评估主要依赖脑电图(EEG)及头颅影像学检查。

EEG 的临床价值在于识别脑损伤严重程度、实时监测脑功能状态及惊厥发作情况, 进行预后分层。颅脑超声具有经济性高、操作便捷、可床旁监测等优势, 但其对颅内损伤的敏感性较低, 存在一定局限性; 头颅 CT 成像快、易获得, 然而因其有辐射及对白质结构分辨率不足, 临床应用受限。目前, HIE 患儿神经损伤评估的首选影像学方法为 MRI, 故对脑电图及颅脑 MRI 的预后价值与相关研究进展进行重点探讨。

(1) 脑电图

早期启动脑电图监测, 能够为亚低温治疗决策提供客观依据, 床旁动态连续监测可指导抗惊厥药物使用, 并获得亚低温治疗及复温后脑电活动的动态演变特征。EEG 背景活动对于 HIE 患儿中具有远期预后分层价值, 且不受亚低温治疗影响[13]。目前, 国内外对于 HIE 脑电背景分度仍未达成共识, 应用较为广泛的依次为 Hellström-Westas、al Naqeeb、Murray 和 Nash 分度法[14]。在出生后早期动态监测中, 脑电图背景模式的演变与临床神经功能评分、MRI 脑损伤评分及短期神经发育结局均具有相关性[15]。EEG 随时间的演变过程较单次脑电图结果能更有效评估 HIE 患儿预后: 生后 24 小时内, 正常或轻度异常的脑电图背景活动, 提示远期神经系统预后良好, 而重度异常背景对不良结局预测价值有限; 生后 1~2 天, 正常脑电图对远期预后良好的预测特异性下降, 而重度异常脑电背景对预后不良的预测价值增加[16]。脑电图背景持续异常与临床症状分度重、MRI 显示脑损伤重有一致性[15], 与死亡、智力障碍及脑瘫等不良预后密切相关。应用脑电图背景评分结合睡眠-觉醒周期动态演变情况, 可进一步提高预测准确性[17]。

脑电图持续监测能够识别临床及亚临床的惊厥发作, 并通过监测数据计算惊厥负荷, 从而对发作频率和持续时间进行量化评估。高惊厥负荷与 HIE 患儿磁共振上脑损伤严重程度独立相关[18] [19]。在接受亚低温治疗的患者中, 高惊厥负荷与患儿 2 月龄神经系统异常发育结局及 BSID-III 认知评分呈负相关[19] [20]。小样本研究表明, 总惊厥负荷与患儿 4 岁时不良结局(包括死亡、癫痫、脑瘫)的发生显著相关, 但 aEEG 背景恢复情况仍是预测个体远期神经发育结局的最强指标[21]。鉴于当前研究数量及样本量有限, 惊厥负荷作为神经功能预后的预测指标仍需通过进一步研究验证其可靠性。此外, 连续脑电图监测技术的临床普及率不足, 故惊厥负荷的实用价值, 需结合当地医疗资源条件评估。

(2) 头颅磁共振

围产期窒息导致脑损伤的程度和位置, 取决于缺氧缺血性事件的严重程度、时机、持续时间和脑成熟程度[22]。头颅磁共振影像上, 缺氧缺血相关的脑病损伤模式与新生儿的胎龄、损伤的性质和严重程度以及干预的时机和疗效相关。MRI 上的损伤模式为我们理解损伤机制和长期预后提供了信息[23] [24]。

现有研究, 尚未就利用 MRI 预测远期神经发育结局的最佳检查时间点达成共识。国内专家共识意见

为生后 2~4 天 DWI 序列有助于早期发现病变, 而晚期关注 T1WI、T2WI 序列对预后判断价值较大[25]。部分研究认为患儿 2~18 月龄 MRI 较新生儿期特异性更高, 而另一些研究指出新生儿期 MRI 敏感性更高, 后续 MRI 可补充损伤演变信息[26], 不同研究间异质性高, 样本量较小。新生儿期 MRI 可根据生后 7 天内完善与否分为早期及晚期, MRI 上显示脑损伤模式可随着时间动态演变, 如部分患儿 MRI 提示晚期新发异常, 既往异常恢复, 或损伤评分分级改变[27]。另有小样本研究将同一患儿早晚期 MRI 结果进行损伤评分对比, 结果显示出高度一致性, 在预测远期神经发育结局上早期 MRI 效能更优, 可能因晚期 MRI 上部分损伤已伪正常化[28]。早期正常的 MRI 对于患儿 30 月龄正常神经发育结局具有较高预测价值(阴性预测值 $\geq 95\%$), 且影像显示的脑损伤模式在接受亚低温治疗及对照组间的预测价值无显著差异[29]。

因人工阅读 MRI 结果有一定主观性, 现有根据不同磁共振序列上的脑损伤表现计算评分的评分系统, 主流的评分系统如 Barkovich 评分、NICHD 评分、Weeke 评分均能判断患儿远期(约 18 个月~2 岁)是否有认知障碍、严重运动功能障碍及死亡等结局, 且 Weeke 评分与语言结局相关[22] [30]。远期随访可以跟踪至 4 岁, 研究显示, Barkovich 评分与患儿 4 岁时粗大运动功能分级系统(GMFCS)的级别正相关, 预测效能显著优于临床指标预测模型[31]。对于轻度 HIE 患儿, 此三种评分系统检测到的微小损伤一致性较好[32], 其中 Weeke 评分因结合 DWI 及 MRS 序列对轻度 HIE 损伤模式识别更敏感[32] [33]。MRI 评分系统较人工阅读影像提高了评价脑损伤的客观性, 仍存在读片者评分不一致的情况[34], 评估者间信度(Inter-rater Reliability)结果提示 Weeke 评分最优, NICHD、Barkovich 评分次之[30], 故应用时需注意评分系统的客观及可重复性。

磁共振波谱(Magnetic Resonance Spectroscopy, MRS)可通过磁共振成像设备检测活体组织中特定代谢物的浓度。多中心前瞻性队列研究(MARBLE 研究)结果表明, MRS 预测远期神经发育结局优于大多数常规磁共振成像结果[35]。有研究提示, MRS 测量的丘脑乳酸/N-乙酰天门冬氨酸水平在预测 HIE 后的不良结果方面优于 MRI 检查[36] [37]。而荟萃分析表明, MRS 影像上 N-乙酰天门冬氨酸(NAA)的绝对浓度水平及其与肌酸(Cr)和胆碱(Cho)的比值(NAA/Cr、NAA/Cho)是对 HIE 患儿不良结局预测最稳定的代谢物指标[38]。

(3) 研究前沿

随着深度学习与 EEG、MRI 技术的融合发展, HIE 的智能分析预后评估体系显著进展。欧洲多中心团队利用机器学习模型, 分析 HIE 患儿生后 12 小时内首个小时的 EEG 监测数据与临床数据结合, 实现了患儿住院期间惊厥发作的风险评估[39]。在神经发育结局预测方面, Lagace 团队及 Montazeri 团队基于深度学习算法, 将脑电图背景转换为 BSN 评分(Brain State of the Newborn), 研究结果显示, BSN 与临床医生评估的 EEG 背景分类及 MRI 脑损伤评分呈现高度一致性。出生前两天内 BSN 的预测价值显著, 能有效预测患儿 18 个月贝利婴幼儿发展量表(Bayley-III)评分[40], 或 4 岁时是否合并脑瘫、癫痫或死亡等不良结局, 性能显著优于传统振幅整合 EEG (aEEG)和 MRI [41]。

深度学习模型可整合头颅磁共振 T1 序列、胎龄和脐带 pH 值, 预测 HIE 患儿 12-24 月龄的不良运动结局, 性能优于逻辑回归模型[42]。机器学习技术, 通过分析 MRI 的结构放射组学特征和几何测量指标, 有效预测 HIE 患儿的 18 个月神经发育结果, 预测覆盖正常发育到严重神经发育障碍的全谱结局, 且效能显著优于人口统计学及临床数据传统模型[43]。根据 MRI 多序列图像及临床数据建立深度学习模型, 预测远期神经发育结局, 效能与放射科医师多读者评分系统相当[44]。

多模态评估可整合影像、电生理、临床数据等多种信息, 显著提升 HIE 预后评估的全面性和准确性。aEEG 与 MRI 结合预测, 预测能力显著高于单独预测[45]。研究显示, 结合患儿生后 24 小时内 EEG 严重异常以及亚低温治疗后 MRI 成像显示至少两个灰质区域异常, 对远期死亡或严重神经系统发育损伤预测特异度达到 99.1% [46], 各研究模型细节见下表 1, 因各研究的神经发育结局不同, 其具体定义见表 2。

Table 1. Summary of included prediction models
表 1. 各预测模型细节

来源	完成随访例数	孕周(周)	HIE临床分度	亚低温治疗	预测因子	MRI/EEG监测时机(日龄)	结局评估(矫正月龄)	结局	统计学方法	最佳模型预测效能	其余模型预测效能
Lally <i>et al.</i>	190	≥36	—	是	MRS、MRI	7 (5~10)	18-24	死亡或中重度NDI	LR	NAA 浓度: AUC = 0.99 (0.94~1.00)	MRI PLIC 评分: AUC = 0.82 (0.76~0.87)
Wu <i>et al.</i>	391	≥36	中重度	是	MRI 损伤评分、MRS 乳酸/NAA 比值	4.5~5.8	24	死亡或 NDI 分级	Proportional odds regression	乳酸/NAA: aOR = 1.6 (1.4, 1.8)	MRI 损伤评分: aOR 1.06 (1.05, 1.07)
Montazeri <i>et al.</i>	80	>36	中重度	—	BSN	0.85~2	48	神经发育结局分类	DL	脑瘫与癫痫 AUC (88.1%~92.7%), 死亡 AUC (96.7%~98.9%), 脑瘫 AUC (78.3%~67.3%)	—
Vesoulis <i>et al.</i>	117	≥36	中重度	是	MRI、临床数据	5 (4~7)	12-24	运动功能障碍	XGBoost、LR	DL: 总体准确率 85%; AUC = 0.75	LR: 总体准确率 80%; AUC = 0.62
Lewis <i>et al.</i>	286	≥35	—	是	MRI 放射组学测量临床数据	4~7	18	Bayley-III 评分	Elastic-Net penalized linear regression	MRI: r = 0.492 (0.365~0.601); MAE = 0.704 ^a	临床数据: r = 0.165 (0.117~0.212); MAE = 0.791 ^a
Chaudhari <i>et al.</i>	414	≥37	中重度	—	多序列 MRI、基本临床变量	4 (3~5)	24	死亡或 NDI	CNN	AUC = 0.74(0.60, 0.86)	—
Steiner <i>et al.</i>	56	≥36	中重度	是	aEEG、NIRS、MRI 损伤评分	5 (4~7)	24	死亡或中重度 NDI	XGBoost、LR	AUC = 0.96~0.99	—
Glass HC <i>et al.</i>	424	≥36	—	是	EEG、MRI、临床数据	4.5~5.6	24	死亡或重度 NDI	CTree	特异度 99.1% (96.8%~99.9%); PPV91.7% (72.8%~97.8%)	—

注: —: 原文未提供; AUC: 曲线下面积; aOR: 调整后优势比; r: 相关系数; MAE: 平均绝对误差; PPV: 阳性预测值。LR: 逻辑回归; Proportional odds regression: 比例优势回归; DL: 深度学习; XGBoost: 极限梯度提升; Elastic-Net penalized linear regression: 弹性网络惩罚线性回归; CNN: 卷积神经网络; Ctree: 条件推断树。NDI (Neurodevelopmental Impairment): 神经发育障碍。注释 a: 处为 Bayley-III 大运动评分相关预测数据。

Table 2. Outcome definitions in included studies
表 2. 各研究结局定义

来源	结局定义
Lally <i>et al.</i>	重度 NDI: 满足 Bayley-III 认知或语言综合评分 < 70 或 GMFCS 3~5 级或需助听器的听力障碍或失明; 中度 NDI: 同时满足 Bayley-III 认知或语言综合评分在 70~84 分伴以下任一表现: GMFCS 2 级; 无助听器需求的听力障碍; 持续性癫痫发作。
Wu <i>et al.</i>	结局分类: 死亡、中重度 NDI (即 GMFCS 水平为 1 且合并脑瘫, GMFCS 水平 ≥ 2, 四肢瘫, 或 BSID-III 认知评分 < 85)、轻度损害(即不符合中重度损伤标准)、无损害
Montazeri <i>et al.</i>	结局分类: 无明显 NDI、脑瘫、脑瘫伴癫痫、死亡

续表

Vesoulis <i>et al.</i>	不良运动结局: 12~24 个月时 Bayley-III 运动评分 < 85 或 AIMS < P10
Lewis <i>et al.</i>	18 月龄时 Bayley-III 7 个不同结局得分: 认知、接受性语言、表达性语言、复合语言、大运动、精细运动、复合运动。
Chaudhari <i>et al.</i>	NDI: 脑性瘫痪, GMFCS 等级 ≥ 1 , BSID-III 认知评分 < 90
Steiner <i>et al.</i>	Ocnorm 组: 结局正常或轻度残疾的婴儿(Bayley-III ≥ 70), OCpath 组: 中重度残疾(Bayley-III < 70)及死亡婴儿。
Glass HC <i>et al.</i>	重度 NDI: Bayley-III 认知评分 < 70 分, GMFCS ≥ 3 分或四肢瘫痪。

综上所述, 胎心监护能有效完成 HIE 患儿的早期监测、筛查, 若能结合计算机化分析、机器学习方法能进一步提高判断准确度。脑电图及头颅磁共振是评估远期神经系统预后的可靠指标, 目前脑电图背景的动态演变、头颅磁共振评分系统的预测效能较高。而惊厥负荷在各研究中计算方式差异大, 且仅凭借惊厥负荷对预后的解释力有限。磁共振波谱定量分析对于代谢物及代谢物比值的最佳选择尚无统一结论。结合机器学习等算法、进行多模态评估有望进一步提高预测准确度, 但目前仍缺乏多中心、大样本量研究, 且临床监测中的脑电图持续监测时间、头颅磁共振完善时机等仍需进一步统一, 能否开展也受到各个中心具体条件限制。推进预后评估工作, 有利于 HIE 患儿长期随访、个性化管理, 提高患儿及其家庭的生活质量。

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