·专题综述·

儿童后颅窝肿瘤手术后小脑性缄默综合征研究进展

杨伟 葛明

【摘要】 小脑性缄默综合征是儿童后颅窝肿瘤手术后的常见并发症，在不同病理类型肿瘤中的发生率存在较大差异（髓母细胞瘤最高，占24%～30%）。发病机制尚未阐明，认为与小脑-大脑回路损害、小脑顶核-中脑导水管周围灰质损害和脑网络改变相关。基于小脑性缄默综合征危险因素构建的预测模型尚未展现出预期的稳定性，仍未推广至临床。药物治疗主要基于临床经验，但疗效有待验证，故目前缺乏明确的有效治疗方法；非药物治疗如物理治疗、作业疗法和言语治疗，对改善远期生活质量有一定作用。本文综述小脑性缄默综合征的发病机制及治疗进展，未来研究应致力于探究小脑性缄默综合征的病理生理学机制、构建更准确的预测模型、制定个性化治疗方案，改善患儿远期预后。

【关键词】 幕下肿瘤； 颅窝，后； 缄默症； 小脑； 手术后并发症； 儿童； 综述

Advances on cerebellar mutism syndrome in children after posterior fossa tumor surgery

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【Abstract】 Cerebellar mutism syndrome (CMS) is a prevalent postoperative complication in children following posterior fossa tumor surgery, with a significantly variable incidence rate across different pathological types of tumors, being highest in medulloblastoma (24%-30%). The pathogenesis of CMS remains to be elucidated, but it is believed to be associated with damage to the cerebellocerebral circuits, harm to the fastigial nuclei of cerebellum and periaqueductal gray matter of the midbrain, and alterations in brain networks. Predictive models constructed based on the risk factors of CMS have not yet demonstrated the anticipated stability and have not been widely adopted in clinical settings. Pharmacological treatments are primarily based on clinical experience, yet their efficacy requires further validation, hence there is currently a lack of a clearly effective treatment method; non-pharmacological treatments, such as physical therapy, occupational therapy, and speech therapy, have shown some effect on improving the long-term quality of life. This review summarizes the pathogenesis and therapeutic advances of CMS, and future research should be dedicated to exploring the pathophysiological mechanisms of CMS, constructing more accurate predictive models, devising personalized treatment plans, and enhancing the long-term prognosis for children.

【Key words】 Infratentorial neoplasms; Cranial fossa, posterior; Mutism; Cerebellum; Postoperative complications; Child; Review

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儿童后颅窝肿瘤手术后小脑性缄默综合征又称小脑性缄默综合征（CMS），是儿童后颅窝肿瘤手术后的最常见并发症。小脑性缄默综合征以语言障碍为核心临床表现，其他功能障碍还包括肌张力降低、不自主运动、共济失调、咀嚼和吞咽障碍、情绪和性格改变、认知功能障碍等，其中语言障碍包括完全缄默和语言减少[1]，缄默可发生于术后即刻，也可在术后1周内任意时间点逐渐显现[2]。绝大多

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数小脑性缄默综合征患儿伴肌张力障碍，肌张力降低可局限于单侧肢体，也可为全身性。共济失调十分常见，而不自主运动、咀嚼和吞咽障碍并不一定发生。情绪改变可表现为躁狂、淡漠或某些情况下无明显变化；性格急躁改变常见于远期随访患儿[3]。文献报道的小脑性缄默综合征发生率差异较大，为8%～39%[4]；来自首都医科大学附属北京儿童医院的数据显示，小脑性缄默综合征占全部后颅窝肿瘤手术患儿的25%，且不同肿瘤类型发生小脑性缄默综合征的比例存在较大差异[5-6]；髓母细胞瘤比例最高（24%～30%），星形细胞瘤则几乎不发生[7-9]。此外，小脑性缄默综合征的临床表现存在较大异质性，目前尚无明确的临床诊断工具，可能导致各研究中心的诊断存有差异，亦是文献报道其发生率不同的原因[10]。既往研究显示，髓母细胞瘤、肿瘤位于中线结构、肿瘤侵犯脑干是术后发生小脑性缄默综合征的危险因素，而肿瘤体积、术前脑积水和手术入路与小脑性缄默综合征的关系则仍存在不同观点[8-9]。有学者提出，经膜髓帆（小脑延髓裂）入路可避免手术损伤小脑蚓，降低小脑性缄默综合征风险[11]；但后经大样本和欧洲多中心研究证实，经小脑蚓造瘘入路与经小脑延髓裂入路手术后小脑性缄默综合征发生率并无明显差异[4,12-14]。近期研究成果揭示髓母细胞瘤分子分型与小脑性缄默综合征的相关性，SHH活化型发生率较低，WNT活化型和G3/4型则相对较高[8]。并推测这种差异可能源于不同分子分型髓母细胞瘤的起源部位不同，SHH活化型多起源于小脑半球，其他分子分型则多起源于中线结构，更易侵犯小脑性缄默综合征相关神经结构。此外，肿瘤恶性程度也是术后发生小脑性缄默综合征的影响因素，高级别肿瘤与更高的发生风险相关，但其确切机制尚未阐明[4]。本文拟对小脑性缄默综合征的发病机制、预测模型和治疗进展进行综述，以为临床进一步研究小脑性缄默综合征提供思路。

一、小脑性缄默综合征的发病机制

1. 小脑-大脑回路假说　小脑-大脑回路通过连接小脑与大脑之间的纤维路径在神经网络信息传递中发挥关键作用。小脑小叶Ⅰ～Ⅳ和Ⅸ通过小脑传出通路与初级运动皮质（M1）、辅助运动区（SMA）和感觉中枢相联系[15]，大脑通过小脑中脚与小脑Crus Ⅰ～Ⅱ和小脑小叶Ⅶb～Ⅷ相联系。手术损伤小脑传出通路可以使大脑运动皮质失去小脑的兴奋性传入，导致小脑性缄默综合征[16]。研究显示，小脑上脚损伤与小脑性缄默综合征相关[17-18]，且小脑-大脑回路损伤程度与缄默持续时间相关[19]。右侧小脑通路与左侧大脑额叶相连，后者在语言形成和表达中具有重要作用，故其损伤与缄默相关[17]。亦有研究显示，双侧或仅左侧小脑上脚损伤与小脑性缄默综合征相关[16,18]。此外，小脑中脚和齿状核损伤在小脑性缄默综合征中的作用尚存争议[19-20]。因此认为，小脑-大脑回路损伤与小脑性缄默综合征的关系有待进一步明确。

2. 小脑顶核-中脑导水管周围灰质假说　基于体素病变症状映射（VLSM）研究显示，小脑下蚓和顶核损伤与小脑性缄默综合征相关[21]。顶核与脑干、下丘脑和边缘系统之间存在广泛联系，调节循环功能、呼吸功能、情绪、认知功能和行为等，还通过小脑上脚调节姿势控制和运动。有研究显示，小脑性缄默综合征急性期中脑导水管周围灰质与Broca区和胼胝体上内侧额叶皮质（sMFC）功能连接（FC）减弱，但可随着缄默症状缓解而逐渐增强[22]。胼胝体上内侧额叶皮质包括前扣带回皮质（ACC）和辅助运动区，涉及运动规划和执行[23]、情感和认知控制[24]、昼夜节律调节[25]。小脑性缄默综合征患儿右侧小脑半球和左侧大脑腹内侧前额皮质（VMPFC）功能连接增强，且与小脑上脚损伤无关联性[22]，这一结论与小脑-大脑回路假说相悖。腹内侧前额皮质主要与高级认知功能相关，包括情感调节和决策等[26]。上述研究提示小脑性缄默综合征存在广泛的脑网络改变，且这些改变与缄默后小脑相关学习的补偿机制有关。因此认为，小脑顶核-中脑导水管周围灰质损伤可能与短暂性缄默相关，而小脑-大脑回路损伤则可能与小脑运动和认知功能障碍相关，但是由于缺乏术前静息态fMRI研究，目前尚不清楚小脑性缄默综合征与非小脑性缄默综合征患儿术前是否存在静息态功能连接的差异。

3. 脑网路假说　研究显示，孤独症谱系障碍（ASD）存在小脑与大脑功能连接改变[27]；齿状核、小脑下蚓（Lobule Ⅸ）、Crus Ⅰ～Ⅱ、小脑半球Lobule Ⅵ和Ⅷb结构异常或功能下降与孤独症谱系障碍相关[27-29]。笔者在临床实践中曾遇到小脑蚓肿瘤患儿术前存在孤独症倾向，术后孤独症谱系障碍相关症状明显减轻。小脑性缄默综合征患者以男性多见，与孤独症谱系障碍好发于男性相一致[30-31]。上述证据提示孤独症谱系障碍与小脑性缄默综合征存在

潜在联系。一项针对健康成人、儿童和孤独症谱系障碍患者的静息态fMRI研究显示，小脑性缄默综合征与孤独症谱系障碍可能共享相似的脑网络，且小脑性缄默综合征相关脑网络改变可以预测孤独症谱系障碍严重程度[32]。这一发现为理解小脑性缄默综合征的病理生理学机制提供了新的思路，提示小脑性缄默综合征与孤独症谱系障碍之间存在潜在的相似功能连接；同时，成人与儿童之间的小脑性缄默综合征相关体素构成的脑网络差异，可为小脑性缄默综合征通常不发生于成人提供合理解释。

二、小脑性缄默综合征的预测模型

小脑性缄默综合征的发病机制迄今尚未阐明，故无有效预防措施。术前预测小脑性缄默综合征的发生风险可以为患者和临床医师提供十分有价值的信息。2018年，Liu等[20]首先提出基于决策树（DT）的小脑性缄默综合征预测模型，该模型纳入年龄（≥12.4岁）、肿瘤部位、双侧小脑中脚和齿状核侵犯作为决策树的节点，模型预测结果分为小脑性缄默综合征高风险、中风险和低风险，其最终预测准确率达88.8%，但是由于模型的输入信息需要资深影像科医师判断，且不同医师之间可能出现不同判断结果，导致模型的鲁棒性较差。2020年，Bae等[33]提出Rotterdam预测模型，在Liu等的基础上增加肿瘤压迫脑干、小脑上脚侵犯、影像学诊断髓母细胞瘤，并剔除年龄因素，该模型基于Logistic回归（LR）算法，模型预测结果分为小脑性缄默综合征高风险、中风险和低风险，最终输出结果与Liu等相似。该模型于2023年由Bush等[34]进一步验证，其预测效能明显下降，预测的准确率由87%降至60%。一方面说明基于主观判断的因素易受主观因素的干扰而影响模型的稳定性，另一方面也提示手术因素在小脑性缄默综合征的发病中发挥一定作用。然而目前的预测模型均未纳入手术因素。2022年，Sidpra等[35]提出基于人工神经网络（ANN）的预测模型（https://amarcu5. github. io/cerebellar-mutism-prediction/calc.htm），同样利用人工判读的影像学指标和临床特征建模，需输入41个临床参数才能进行预测，因算法的改进，其预测效能较Liu等和Bae等的模型显著提高，准确率＞90%。然而，上述预测模型所纳入变量均为人工判读结果，使得模型的鲁棒性受到限制。首都医科大学附属北京儿童医院分别基于影像组学和基于体素病变症状映射构建小脑性缄默综合征预测模型，影像组学是利用计算机技术提取肿瘤影像学特征，具有标准化、可重复、可量化、信息丰富的优点，使得同一患者在不同医疗中心所提取的影像学特征完全一致，克服既往研究的不足，两种模型在验证集中的准确率分别达78%和73%[36-37]，提示肿瘤影像组学特征和位置特征可以很好地预测小脑性缄默综合征，为未来预测模型研究提供新的方向。

三、小脑性缄默综合征的治疗

小脑性缄默综合征的治疗主要基于既往临床经验，包括药物治疗和非药物治疗。药物治疗有咪达唑仑、唑吡坦、氯硝西泮、地西泮、氟西汀、利培酮、舍曲林、溴隐亭、阿立哌唑、莫达非尼、氟哌啶醇等，这些药物通过促进γ-氨基丁酸（GABA）能受体激活、抑制多巴胺能受体和5-羟色胺能受体激活或抑制5-羟色胺再摄取，发挥治疗作用。临床最常用的药物是溴隐亭[38-43]，可缓解临床症状，大多数患儿给药后48小时内恢复[44]，治疗时间持续数周至数月。Amor-García等[43]应用溴隐亭治疗小脑性缄默综合征，以1.25 mg为起始剂量（1次/8 h），逐渐增量至7.50 mg（1次/8 h），取得良好疗效。Nicita等[41]报告1例小脑性缄默综合征患儿静脉注射咪达唑仑（0.10 mg/kg）后，缄默症状短暂性改善。Shyu等[45]认为，每日睡前服用唑吡坦2.50 mg可缓解小脑性缄默综合征症状。Amor-García等[43]和Akhaddar等[46]先后应用氟西汀（20 mg/d）或氟西汀（10 mg/d）联合溴隐亭（15 mg/次、1次/8 h）治疗小脑性缄默综合征，均获得较好疗效。目前关于小脑性缄默综合征药物治疗的报道仅为病例报道，缺少大样本队列研究，其疗效待进一步验证，其药理学和药效学机制及药代动力学尚待进一步探究。非药物治疗包括物理治疗、作业疗法和言语治疗，在小脑性缄默综合征的康复中发挥一定作用，可以改善患儿远期生活质量，然而目前相关研究较少[44]。语言监测评估有助于判定缄默症状缓解后的言语障碍类型，从而指导缄默后期语言功能康复，然而目前缺乏对小脑性缄默综合征语言功能评估的系统性研究，其康复治疗尚无统一的临床指导方案。

综上所述，小脑性缄默综合征已成为儿童后颅窝肿瘤手术后的最大挑战，对患儿远期生活质量造成严重不良影响，包括运动功能、情绪和认知功能等[45-46]。尽管这一疾病最早在1958年即被报道，但其发病机制迄今尚未阐明[47]，进一步细致量化小脑性缄默综合征的临床特征，包括语言障碍类型、神

经心理学评估等是亟待解决的问题[48]。既往一直将小脑性缄默综合征作为一种疾病综合体，不利于阐明其神经病理学机制，未来研究应单独探讨小脑性缄默综合征的不同功能损害，从而将相应的功能损害与神经功能改变相对应，以利于更加深刻的认识小脑功能分区，从而在后颅窝肿瘤手术中避免损伤重要结构[22]。

利益冲突 无

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