



· 专家述评 ·



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转移性儿童甲状腺癌的遗传学特征和预后

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[摘要] 甲状腺癌的发病率随着年龄的增长而增加，虽然儿童甲状腺癌的发病率远低于成人，但在世界范围内甲状腺癌已经成为0~14岁儿童第5大常见癌症以及青少年最常见的癌症。不同于成人患者，目前普遍认为儿童甲状腺癌发病率的增加更有可能是基因或环境因素所致，并且儿童甲状腺癌在发病时往往更趋近于晚期，其复发率也远高于成人甲状腺癌，但是儿童甲状腺癌的分子病理学特征与肿瘤转移的关系仍有待进一步明确。本文将结合国内外研究进行综述，重点讨论转移性儿童甲状腺癌的遗传学特征，为研究者和临床医师针对儿童甲状腺癌的基础研究和肿瘤防治提供参考。

[关键词] 儿童甲状腺癌；肿瘤转移；分子病理；预后

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[Abstract] The incidence rate of thyroid cancer increases with age. Although the incidence rate of thyroid cancer in children is far lower than in adults, thyroid cancer has become the fifth most common cancer among children aged 0-14 and the most common cancer among adolescents worldwide. Unlike thyroid cancer in adults, the increase in the incidence of thyroid cancer in children is

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more likely to be caused by genetic or environmental factors. Moreover, thyroid cancer in children tends to be late stage, and the recurrence rate is much higher than in adults. However, the relationship between molecular pathological characteristics and metastasis of thyroid cancer in children still needs to be further clarified. This review focused on the genetic changes of metastatic thyroid cancer in children in order to provide the reference for researchers and clinicians to better understand basic research, prevention and treatment of thyroid cancer in children.

[**Key words**] Childhood thyroid carcinoma; Metastasis; Molecular pathology; Prognosis

1 儿童甲状腺癌的流行病学特点

儿童及青少年肿瘤的流行病学研究显示, 甲状腺癌的发病率在世界范围内逐年增加, 虽然发病率远低于成人, 但甲状腺癌已经成为0~14岁儿童第5大常见癌症以及青少年最常见的癌症^[1]。美国数据显示, 按年龄分层分析每年儿童及青少年癌症的发病率为0.43/1 000 000 (5~9岁)、3.50/1 000 000 (10~14岁)和15.16/1 000 000 (15~19岁)^[1-2]。目前儿童发病率升高的原因尚不明确, 尽管大量研究^[3-5]表明, 癌症早筛是成人甲状腺癌发病率逐年增加的重要原因, 然而儿童及青少年通常没有涵盖在早筛人群当中, 因而发病率的增加更有可能是基因或环境因素所致。不同于成人甲状腺癌, 儿童患者发病时往往是晚期, 并且其复发率要高于成人甲状腺癌, 儿童患者初诊发生远处转移的概率为7%~30%, 而成人患者只有2%~9%, 大多数远处转移部位为肺, 但脑、软组织和骨转移也有少数病例报告, 然而儿童甲状腺癌的分子病理学特征与复发的关系仍有待进一步研究^[6-8]。

2 儿童甲状腺癌的危险因素

儿童甲状腺癌的病理学类型与成人基本一致, 女性多于男性, 且以甲状腺乳头状癌 (papillary thyroid carcinoma, PTC) 为主, 约为92.2%, 甲状腺滤泡癌 (follicular thyroid carcinoma, FTC) 和甲状腺髓样癌 (medullary thyroid carcinoma, MTC) 仅占7.8%, PTC中较常见的亚型包括实体型、滤泡型和弥漫性硬化型^[9]。与成人相比, 儿童患者的特点包括病灶大、多灶性、易累及双侧腺体、早期颈部软组织受侵、早期颈部淋巴结转移、远处转移更多见 (最常发生在肺部) 及术后复发率较高等^[10-12]。

电离辐射与儿童甲状腺癌的关系密切, 儿

童时期的甲状腺对辐射非常敏感, 切尔诺贝利严重核污染地区的发病率高达40%, 且每年的发病率都在上升, 尤其是年龄为0~4岁的高暴露人群在10年后发病率明显增加^[13-14]。流行病学研究^[15-16]发现, 医疗诊断和治疗是另一个高危因素, 儿童因其他癌症接受放疗后的甲状腺癌发病率明显增加。另外, 儿童甲状腺癌与自身免疫性甲状腺疾病有关, 患有桥本甲状腺炎的患者发病率约为0.67%, 高于一般儿童人群的发病率 (0.02%), 但其具体机制仍不明确。遗传因素同样是高危因素, 遗传性甲状腺癌的发病年龄较小且更具侵袭性, 更容易出现多发病灶和淋巴结转移的现象^[17-19]。

3 转移性儿童甲状腺癌的病理学特征

有研究^[20]显示, 肿瘤大小和甲状腺包膜侵犯是预测淋巴结和远处转移的危险因素, 一般认为儿童PTC肿瘤 ≥ 1 cm是淋巴结转移的高危因素, 而甲状腺包膜侵犯、软组织侵犯等均被认为是肿瘤转移的高危因素 ($P < 0.05$)。通过分析监测、流行病学和最终结果 (Surveillance, Epidemiology, and End Results, SEER) 数据库显示, 儿童甲状腺癌总的淋巴结转移率为26.11%, 与年龄 > 30 岁组相比, 0~10岁组的比值比 (odds ratio, OR) 为7.19 (95% CI: 3.76~13.75), 11~20岁组为3.45 (95% CI: 3.08~3.87), 21~30岁组为2.28 (95% CI: 2.15~2.41); 低龄与总阳性淋巴结增多、术后阳性淋巴结比例增加呈正相关^[21-24]。

4 转移性儿童甲状腺癌的分子遗传学特征

与成人相比, 儿童患者表现出相似的基因突变或融合突变谱, 但突变频率略有差异。目前发现*BRAF*突变和*RET/PTC*重排仍然是最常见的遗传学改变, 并且与儿童甲状腺癌高度相关, 其中*RET/PTC*重排与颈部淋巴结转移的相关性尤为明

显。下面我们将近年来的多项研究^[25-47]结果进行汇总,总结儿童甲状腺癌患者淋巴结转移和远处转移中关键的遗传学改变。

4.1 *BRAF*基因突变

BRAF V600E突变是成人PTC最常见和最特异的遗传学改变,但在儿童患者中的发生率不高,一项纳入138例儿童患者的研究^[27]发现,在突变型病例中,83例(86.5%)出现淋巴结转移,而在野生型病例中,仅有26例(61.9%)出现淋巴结转移。另一项纳入235例患者的研究^[28]显示,儿童患者CD133的表达在淋巴结转移患者中显著增加($P=0.02$),在*BRAF* V600E突变的患者中CD133高表达的患者更多($P=0.03$),提示*BRAF* V600E突变作用复杂,除了能够直接促进肿瘤进展外,还可以连同其他遗传学改变加速肿瘤的转移。另有一项研究^[29]显示,*AGK-BRAF*基因融合与儿童患者初诊时的远处转移和肿瘤多灶性密切相关,提示融合突变也是*BRAF*激活丝裂原激活蛋白激酶(mitogen-activation protein kinase, MAPK)/胞外信号调节激酶(extracellular signal-regulated kinase, ERK)通路的机制之一。

4.2 *RET/PTC*基因重排

*RET*基因重排最早在辐照PTC中被发现,目前已有20余种类型被确定,是成人PTC中第二常见的遗传学改变^[30,31]。*RET/PTC1*和*RET/PTC3*是迄今为止报道最多的两组亚型,且是儿童患者中最常见的遗传学特征^[32]。一项关于复发转移性儿童甲状腺癌的研究^[33]发现,30例有淋巴结转移的患者中,63%的患者存在*BRAF* V600E突变或*RET/PTC*重排($P=0.04$),进一步的突变类型分析显示,12例*BRAF*突变阳性病例中,75%的患者表现出晚期肿瘤的特点(肿瘤>4 cm或癌症已扩散到甲状腺外和淋巴结);12例*RET/PTC*阳性病例均显示包膜外侵或中央/侧方淋巴结转移,并且3例患者有远处转移。通过分析癌症基因组图谱(The Cancer Genome Atlas, TCGA)数据库发现,与*RAS*或*BRAF*突变组相比,*RET/NTRK*基因融合的儿童患者更容易出现晚期淋巴结和远处转移,治疗1年后疾病缓解的可能性更

小^[34]。另外一项纳入9例儿童患者的研究^[35]显示,*RET/PTC*重排与包膜外侵、淋巴结转移显著相关。

4.3 *TERT*基因启动子突变

尽管有研究^[36]显示,*TERT*启动子突变(C228T和C250T)与成人甲状腺癌患者的不良预后相关,但其在儿童患者中似乎很少出现。一项纳入59例样本的研究^[37]显示,唯一1例携带*TERT*启动子突变的患者,同时也伴有*RET/PTC*重排,进一步支持上述结论。

4.4 *NTRK*基因融合突变

尽管在成人患者中已发现*NTRK*基因融合突变与患者的不良预后相关,但是在儿童患者中的报道较少。日本的一项病案研究^[38]发现,1例7岁日本女性患者经基因检测发现*ETV6/NTRK3*重排,组织病理学检查显示为典型的PTC伴颈部淋巴结转移。

4.5 *Pax-8*基因异常表达

正常成人甲状腺和甲状腺癌中均发现*Pax-8*蛋白的表达,但在未分化甲状腺癌中未检测到。一项纳入47例儿童甲状腺癌的研究^[39]发现,*Pax-8*在良恶性病变之间差异无统计学意义($P>0.05$),然而,免疫组织化学检测结果显示,细胞质中*Pax-8*染色强度与肿瘤大小、转移、局部浸润和复发等显著相关,细胞质中高表达*Pax-8*的患者无病生存率显著降低($P=0.0003$)。

4.6 其他融合突变

一项大样本测序研究^[40]的数据显示,儿童甲状腺癌中携带融合突变的肿瘤更可能与区域淋巴结转移相关($P=0.001$),在众多的突变中,除了典型的*RET-CCDC6*、*RET-NCOA4*和*ETV6-NTRK3*基因重排外,还发现了几种罕见融合转录物,包括*AKAP13-RET*、*TRIM27-RET*、*TNIP1-RET*、*SQSTM1-NTRK3*、*TFG-MET*、*TRIM24-MET*、*EML4-ALK*和*TG-THADA*。

4.7 表观遗传学异常

一项纳入113例儿童甲状腺癌的研究^[41]发现,10个miRNA在肿瘤组织中表达异常,其中miR-31-5p、miR-146b-5p、miR-222-3p、miR-375

和miR-551b-3p的高表达与甲状腺内扩散、甲状腺包膜侵犯及淋巴结转移等恶性行为显著相关。

4.8 其他

儿童甲状腺癌患者中D2-40呈现高表达, 且与包膜侵犯、淋巴结转移相关, 提示D2-40检测在儿童甲状腺癌淋巴转移方面有一定的临床价值^[42]。有研究^[43-45]显示, 包括*TSHR*持续高表达、*SLC5A5*表达降低和*TFG/NTRK1*重排参与儿童甲状腺癌的快速进展和早期转移, 此外, 肺转移患者的肿瘤中钠碘同向转运体(sodium/iodide symporter, NIS)的mRNA表达显著降低。一项儿童及青少年PTC远处转移患者的测序分析研究^[46]发现, 基因融合突变(*RET*、*ALK*或*NTRK1*)及染色体22q缺失与远处转移相关, 并且研究者据此建立了用于预测PTC远处转移的血液学模型。甲状腺球蛋白(thyroglobulin, Tg)在甲状腺癌疗效评价及预后预测中具有重要作用, 一项纳入98例经治分化型甲状腺癌(differentiated thyroid cancer, DTC)患者的研究^[47]发现, 19例(19%)有肺转移, 其中17例(89%)在甲状腺切除术后6个月内确诊肺转移, 并且肺转移患者较年轻($P<0.001$), <13岁的患者40%有肺转移, 且原发肿瘤直径较大($P=0.01$), 肺转移患者术后Tg较高($P<0.001$), 11例患者中有10例(91%)的Tg值为2 ng/mL, 100%的患者术前Tg升高(>60 ng/mL), 术后血清Tg水平与治疗反应呈正相关。

5 转移性儿童甲状腺癌的分子靶向治疗

尽管儿童甲状腺癌患者预后良好, 但与成人甲状腺癌具有不同之处, 儿童及青少年甲状腺癌更常出现淋巴结受累、远处转移及术后复发。研究^[48]发现, 患有远处转移(主要为肺转移)的个体平均年龄为10.4岁, 且大多能够检测到致癌融合突变, 这些高频的分子异常如*RET/PTC*重排、*NTRK2*基因融合突变等可能导致肿瘤更容易侵犯周围淋巴管, 发生区域淋巴结转移和肺转移。但即便发生肺部转移, 儿童患者的病死率亦低于年龄>45岁的患者, 可能原因是其肺转移病灶进展缓慢, 且大部分可手术患者对手术和¹³¹I治

疗敏感, 即使初治不可手术患者在经过¹³¹I治疗后, 肺部病灶亦可逐渐缩小甚至消失。鉴于儿童及青少年甲状腺癌的高淋巴结转移发生率及高复发率, 临床上即使面对T₁或T₂期的肿瘤患者, 依然建议行术后¹³¹I治疗^[49-50]。不过, 仍有一部分儿童患者会继续发展为进行性、放射性碘难治性和症状性疾病, 所以对这一类患者进行全面基因分析对指导临床治疗至关重要。

随着甲状腺癌分子生物学研究的蓬勃发展, 许多有效的药物分子作用靶标相继被发现。基于一个或多个靶点研发出的针对这些转移性或难治性甲状腺癌治疗的小分子抑制剂在体内外实验中已被证实安全可靠, 甲状腺癌分子靶向治疗可显著延长晚期甲状腺癌患者的预后生存期, 使广大患者从中受益。然而除了美国食品药品监督管理局(Food and Drug Administration, FDA)加速批准的普雷西替尼(BLU-667)^[51]和塞尔帕替尼(LOXO-292)^[52]用于治疗*RET*突变阳性的晚期或转移性甲状腺髓样癌成年及12岁以上儿童患者以外, 众多临床研究在设计上均没有纳入18岁以下的儿童及青少年患者, 因此对于除MTC外的晚期儿童患者的分子靶向治疗药物多参考成人用药及个案报道。

索拉非尼是第一个被批准用于临床的多靶点治疗药物, 多项研究^[53-54]证实, 索拉非尼治疗碘难治性甲状腺癌患者, 可延缓疾病的进展并延长疾病的无进展生存期。在1例11岁男性甲状腺癌合并弥漫性肺转移致呼吸困难的患者中, 通过索拉非尼400 mg/d的治疗后, 症状改善并进行了手术治疗, 术后维持治疗24个月, 随访无严重不良反应发生^[55]。凡德尼布可有效地治疗晚期MTC并能够延长无进展生存期^[56-57], 一项纳入16例晚期或转移性儿童MTC患者的研究^[58]发现, 客观应答率为47%, 腹泻是主要的剂量限制毒性。乐伐替尼可有效地治疗碘不敏感DTC及晚期MTC^[59-60], 一项纳入3例转移性难治性PTC儿童的研究^[61]显示, 所有患者对乐伐替尼的耐受性良好, 最长持续稳定时间为23个月。除此之外, 依维莫司^[62]、阿帕替尼^[63]等靶向药物也被证实对儿童晚期甲状腺癌具有一定疗效, 随着

新的靶向药物不断涌现,期待更多药物在临床研究中关注儿童患者的治疗,为儿童晚期转移性甲状腺癌的治疗开拓更广阔的空间。

6 结语

儿童及青少年甲状腺癌侵袭性很高,虽然总体存活率较高,但复发转移性晚期患者预后仍较差,且治疗手段有限,随着分子生物学的快速发展,未来期待更多基础研究探索儿童患者的分子生物学异常,从而进一步改进儿童患者的诊断、预后和治疗。

利益冲突声明: 所有作者均声明不存在利益冲突。

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