

. 综 述 .

儿童颅咽管瘤术后复发的影响因素

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【摘要】颅咽管瘤是一种颅内常见的胚胎残余组织来源的良性肿瘤。根据病人年龄、肿瘤形态和生长方式,颅咽管瘤可区分为成釉细胞型和乳头状型。成釉细胞型颅咽管瘤是儿童最常见的中枢神经系统肿瘤之一,高峰年龄为 5~14 岁。儿童颅咽管瘤的 5 年总生存率在 83%~96%,10 年生存率在 65%~100%,20 年平均生存率为 62%。颅咽管瘤的发病率和病死率不仅与原发肿瘤有关,而且与肿瘤复发有关。尽管颅咽管瘤被归类为良性肿瘤,但通常表现为局部侵袭性生长,术后易复发。本文就儿童颅咽管瘤术后复发的影响因素进行总结,为临床提供参考。

【关键词】颅咽管瘤;儿童;术后复发;影响因素

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Factors related to postoperative recurrence of craniopharyngioma in children

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【Abstract】Craniopharyngioma is a common benign tumor in the brain that originates from embryonic residual tissue. Based on the patient's age, tumor morphology and growth characteristics, craniopharyngiomas can be categorized into adamantinomatous and papillary subtypes. Adamantinomatous craniopharyngioma is among the most frequent central nervous system tumors in pediatric patients, with a peak incidence between 5 and 14 years of age. The 5-year overall survival rate for pediatric craniopharyngioma ranges from 83% to 96%, the 10-year survival rate spans from 65% to 100%, and the mean 20-year survival rate is 62%. The incidence and mortality rates of craniopharyngioma are influenced not only by the primary tumor but also by tumor recurrence. Although classified as benign, craniopharyngiomas often display locally invasive growth patterns and have a tendency to recur following surgical resection. This review aims to summarize the factors related to postoperative recurrence of craniopharyngioma in children, providing valuable insights for clinical management.

【Key words】Craniopharyngioma; Children; Postoperative recurrence; Risk factors

颅咽管瘤是一种颅内常见的胚胎残余组织来源的良性肿瘤^[1]。大部分颅咽管瘤位于鞍上区域,通过挤压或侵袭周围视神经、垂体、下丘脑等重要结构,影响神经内分泌功能^[2]。颅咽管瘤为 WHO 分级 I 级,组织学为良性,但通常表现为局部侵袭性生长。在组织学上,颅咽管瘤主要有两种亚型,即成釉细胞型和乳头状型,它们在年龄、发病率、生物学和临床结局上存在差异^[3]。成釉细胞型颅咽管瘤主要发生在儿童,高峰年龄为 5~14 岁^[4]。儿童颅咽管瘤的 5 年总生存率在 83%~96%,10 年生存率在 65%~100%,20 年平均生存率为 62%^[5]。颅咽管瘤的发病率和病死率不仅与原发肿瘤有关,而且与肿瘤的复发有关。颅咽管瘤术后复发时间平均为 3 年^[6]。本文就儿童颅咽管瘤术后复发的影响因素进行总结,为临床提供参考。

1 流行病学因素

1.1 年龄 颅咽管瘤占儿童颅内肿瘤的 1.2%~4.6%。通常,成釉细胞型颅咽管瘤呈双峰年龄分布(5~15 岁和 45~60 岁)。乳头状型颅咽管瘤的高峰年龄在 40~55 岁,儿童较少见^[7]。研究发现,10 岁之前发病的颅咽管瘤伴随较高的肥胖、失明、全垂体功能减退的发生率,而且只有 40.7% 的患儿有良好的学业表现或职业生涯;晚发病人中,72.4% 的病人有良好的学业表现或职业生涯^[8]。这提示发病时间越早对病人越不利,早发与儿童颅咽管瘤复发有较高相关性。

1.2 性别 有研究显示,男性与颅咽管瘤复发风险增加有关。但也有研究认为男性与颅咽管瘤复发之间无相关性^[6]。由于无合理的病理机制来解释这种男女复发率的差异,且相关数据不一致,因此无法确定男性与复发风险增加之间是否存在相关性^[6]。

2 肿瘤的形态特征

2.1 肿瘤大小 关于肿瘤大小对肿瘤复发率的影响,

文献报道并不一致。早在 1985 年,Al-Mefty 等^[9]研究认为,直径>5 cm 的肿瘤为巨大颅咽管瘤。也有学者将直径>4 cm 的肿瘤视为巨大颅咽管瘤^[10]。Hu 等^[11]研究发现,肿瘤直径>5 cm 是颅咽管瘤术后复发的影响因素($OR=2.144$; 95% CI 1.381~3.329),肿瘤越大越易复发。Sadhasivam 等^[12]研究指出,肿瘤大小是预测颅咽管瘤术后预后的重要指标,并且巨大肿瘤病人的全切除率低于小肿瘤,但巨大肿瘤的复发率、无进展生存期、总生存期与非巨大肿瘤病人相当。

2.2 肿瘤位置 有研究根据肿瘤起源及肿瘤与蛛网膜的关系进行分类,将颅咽管瘤分为 Q 型、S 型和 T 型:Q 型起源的位置在鞍膈以下,S 型起源的位置在垂体柄的蛛网膜内和蛛网膜外段,T 型起源的位置在垂体柄袖套间段;Q 型与 S/T 型的主要区别在于是否存在垂体窝扩大或肿瘤是否位于鞍膈上方,S 型与 T 型的主要区别在于垂体柄位于肿瘤的旁边或底部,肿瘤延伸至蛛网膜下腔或第三脑室,蛛网膜是否与基底结节及肿瘤分离^[13]。研究显示,S 型颅咽管瘤术后复发率明显低于 Q 型和 T 型^[11]。Park 等^[14]研究显示,鞍膈上、鞍膈下的颅咽管瘤术后复发危险明显增加。Sadhasivam 等^[15]报道视交叉后颅咽管瘤与术后垂体功能低下和下丘脑发病率较高有关,但与肿瘤术后复发无明显关系。

2.3 肿瘤质地 肿瘤质地,即囊性、实性或囊性/实性混合肿瘤,与颅咽管瘤复发的风险相关。针对儿童颅咽管瘤的研究表明,与实性颅咽管瘤相比,囊性颅咽管瘤术后复发率更高,这可能与手术难以取出完整的囊性肿瘤包膜有关^[6,16]。

3 肿瘤组织学特征

颅咽管瘤主要有两种病理亚型,即乳头状型颅咽管瘤和成釉细胞型颅咽管瘤,二者不仅在发病率和年龄分布上存在差异,而且在病理特征上也存在差异^[3]。成釉细胞型颅咽管瘤比乳头状型颅咽管瘤更容易复发,原因尚不清楚^[17]。可能的原因有:首先,乳头状型颅咽管瘤很少钙化,通常边界清晰,而成釉细胞型颅咽管瘤以囊性多见,且浸润周围结构的几率较高^[18];其次,钙化的颅咽管瘤往往与较低的肿瘤切除率相关,导致肿瘤残余,增加肿瘤复发的风险;再次,颅咽管瘤侵袭周围结构,特别是下丘脑的严重程度也可能影响肿瘤切除率及术后复发率^[19];最后,成釉细胞型颅咽管瘤和乳头状型颅咽管瘤之间特定分子表达的差异导致肿瘤复发的风险不一样,例如,主要积聚在成釉细胞型颅咽管瘤细胞中的

β -catenin 与更具侵袭性的颅咽管瘤行为相关,使成釉细胞型颅咽管瘤具有更高的复发风险^[16,20]。Yan 等^[21]也认为,钙化增加了成釉细胞型颅咽管瘤切除的难度,并增加了并发症和复发的风险,成釉细胞型颅咽管瘤钙化可能是成骨分化的结果,这与成骨和牙龈发育中的钙沉积相似。成釉细胞型颅咽管瘤存在的涡状排列与复发风险增加显著相关,涡状排列与 β -catenin 基因的突变有关。超过 70% 的成釉细胞型颅咽管瘤具有 β -catenin 基因的突变, β -catenin 不能被降解,导致目标基因的激活和转录,驱动肿瘤发生、发展,因此,涡状排列提示致瘤活性^[16]。

Ki-67 是颅咽管瘤复发研究最多的分子标志物,但报道结果不一致。Ki-67 是一种核蛋白,与肿瘤增殖活性、侵袭性相关,Ki-67 指数与预后相关^[22]。恶性颅咽管瘤 Ki-67 表达水平升高^[16]。Xu 等^[23]检测 59 例原发性颅咽管瘤 Ki-67 表达水平,发现高 Ki-67($\geq 5\%$)与肿瘤复发存在显著关联。Moszczyńska 等^[24]研究显示,复发和未复发颅咽管瘤的 Ki-67 表达水平没有统计学差异,但与原发性肿瘤相比,复发性肿瘤 Ki-67 值更高。

p53 基因是一种抑癌基因,定位于人类染色体 17p13.1,编码 393 个氨基酸组成的 53 kD 的核内磷酸化蛋白,被称为 P53 蛋白。研究发现,复发颅咽管瘤 P53 的表达水平明显高于原发性颅咽管瘤^[25]。这提示 P53 表达与颅咽管瘤复发有关。

BRAF V600E 及 CTNNB1 基因突变与成釉细胞型颅咽管瘤密切相关,CTNNB1 基因编码 β -catenin,一旦突变,则影响 β -catenin 蛋白稳定性,使 β -catenin 不能被有效降解,导致其核积累而激活 Wnt 信号通路,这与肿瘤的发展密切相关^[26-29]。成釉细胞型颅咽管瘤比乳头状型颅咽管瘤更容易复发^[16]。这提示 BRAF V600E 及 CTNNB1 基因突变与颅咽管瘤复发的有关。

血管内皮生长因子(vascular endothelial growth factor, VEGF)及缺氧诱导因子 1 α (hypoxia-inducible factor 1 α , HIF1 α)调节血管生成,是肿瘤生长所必需的。HIF1 α 是一种介导细胞对缺氧反应的转录因子,在肿瘤细胞中表达失调^[16]。研究表明,无论组织病理亚型如何,颅咽管瘤复发与较高的 VEGF 和 HIF1 α 表达相关,表明 VEGF 可能在新血管生成和肿瘤再生中发挥作用^[6]。

视黄酸受体(retinoic acid receptor, RAR)使参与上皮成熟和分化的核受体,由 RAR α 、RAR β 和 RAR γ 三种亚型组成。RAR 表达水平与颅咽管瘤复发率有

关,低表达RAR-β和高表达RAR-γ的颅咽管瘤更容易在手术切除后2年内复发,这可能与RAR调控组织蛋白酶表达有关^[6,16]。

4 激素

生长激素(growth hormone, GH)和胰岛素样生长因子(insulin-like growth factor, IGF)可通过减少肿瘤细胞快速进展过程中DNA修复的时间来增加突变的数量。实体肿瘤和血液系统恶性肿瘤与GH、IGF-I的局部产生、GH/IGF系统受体的表达正常或改变以及GH和IGF-I诱导的miRNA失调有关^[30]。GH受体高表达的颅咽管瘤具有更高的增殖潜能。IGF-I受体在成釉细胞型颅咽管瘤中比在乳头状型颅咽管瘤中表达更丰富,这提示IGF-I受体参与这类肿瘤的复发^[16]。此外雌激素受体(estrogen receptor, ER)和孕酮受体(progesterone receptor, PR)阴性颅咽管瘤术后复发率明显增加^[31]。

5 治疗方法

5.1 肿瘤切除程度 手术是颅咽管瘤主要的治疗方法,但最佳的手术治疗方案仍然存在争议^[32]。肿瘤以及瘤旁正常组织的完整切除是降低术后复发率的有效方法,肿瘤全切除术后复发率较肿瘤部分切除术后复发率明显降低^[12,33]。但Ji等^[34]研究显示肿瘤全切除与异位复发无明显关系,异位复发性颅咽管瘤的主要病理学是成釉细胞型颅咽管瘤。

垂体柄连接垂体和下丘脑,是维持下丘脑-垂体功能的重要解剖基础。垂体柄的损伤,无论是病理性,还是医源性,都会损害内分泌功能,并严重影响病人的生活质量。然而,术中保留垂体柄可能会增加颅咽管瘤的复发风险^[33,35]。

5.2 辅助放疗 术后放疗显著降低次全切除术后肿瘤复发风险。儿童颅咽管瘤次全切除术后接受放疗的复发率与全切除术后病人相似。肿瘤全切除通常伴有内分泌功能障碍和下丘脑损伤,从而增加并发症。因此,有学者主张采用不太激进的手术方法,术后辅以放疗。近年来,越来越多的学者倾向于对复杂颅咽管瘤进行次全切除,然后进行放疗,以最大限度地提高病人生活质量,同时实现肿瘤控制^[16]。

5.3 GH代替治疗 适用于儿童期发病的颅咽管瘤引起的生长激素缺乏症儿童。颅咽管瘤术后患儿可能存在GH缺乏症,并出现生长发育迟缓,予以GH代替治疗,可促进生长发育。但GH代替治疗会激活GH/IGF-1轴,增加血液IGF-1浓度,尽管患儿生长

发育获益非常明显,但也可能有潜在的增加颅咽管瘤复发风险^[36,37]。

6 小结与展望

在过去几十年期间,尽管针对儿童颅咽管瘤复发的研究很多,但很多研究结果存在矛盾,原因可能是颅咽管瘤形态、大小、侵袭性、组织学特征、分子特征等方面存在异质性。此外,病人年龄较小、囊性肿瘤体积较大、与周围组织结构紧密粘连、诊断时出现特定临床表现、组织学存在旋涡状排列以及某些特定的分子特征均与颅咽管瘤复发相关。今后,可开展多中心前瞻性研究探讨颅咽管瘤复发的病理机制。这不仅有助于识别颅咽管瘤复发的风险因素,从而辅助制定最佳治疗策略,还将指导开发新的靶向治疗方法,与手术、放疗相结合,有望提高颅咽管瘤儿童无复发生存率,并最终改善患儿的长期生活质量。

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