

· 综述 ·

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颅咽管瘤相关肝脏疾病的致病机制及治疗

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摘要: 颅咽管瘤患者是代谢相关脂肪性肝病及其严重并发症的高危人群,但这一关联在临床上常被忽视,相关系统性总结匮乏。本文系统回顾了颅咽管瘤相关肝脏疾病的临床谱系与流行病学特征,重点分析了其发病的核心机制,并总结了当前以预防下丘脑损伤为导向的肿瘤治疗策略,明确了建立多学科协作诊疗模式并实施早期干预是改善预后的关键。未来研究应致力于深入解析下丘脑损伤导致代谢紊乱的精确通路,并以此为基础开发靶向治疗,为从根本上改变此类患者的临床结局提供新方向。

关键词: 颅咽管瘤; 代谢相关脂肪性肝病; 下丘脑疾病; 生长激素; 治疗学

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Pathogenesis and treatment of craniopharyngioma-related liver diseases

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Abstract: Patients with craniopharyngioma are at a high risk of developing metabolic dysfunction-associated fatty liver disease and its severe complications, yet this association is often neglected in clinical practice, with a lack of systematic reviews. This article systematically reviews the clinical spectrum and epidemiological characteristics of liver diseases associated with craniopharyngioma, with a focus on their core pathogenic mechanisms, and it also summarizes current tumor treatment strategies aimed at preventing hypothalamic injury and highlights that establishing a multidisciplinary collaborative diagnosis and treatment model and implementing early intervention are key to improving prognosis. Future research should focus on elucidating the precise pathways through which hypothalamic injury leads to metabolic disturbances, thereby facilitating the development of targeted therapies, in order to provide new directions for fundamentally improving the clinical outcomes of these patients.

Key words: Craniopharyngioma; Metabolic Dysfunction-Associated Fatty Liver Disease; Hypothalamic Diseases; Growth Hormone; Therapeutics

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颅咽管瘤是由Rathke囊或颅咽管残存的胚胎上皮细胞化生而来的良性肿瘤^[1],占成人颅内肿瘤的1.2%~4.6%,占儿童颅内肿瘤的5.6%~15.0%,占儿童鞍区肿瘤的54%。组织学上,颅咽管瘤分为两种亚型:造釉细胞型颅咽管瘤和乳头型颅咽管瘤,两者在发病年龄和分

子机制上存在差异。造釉细胞型颅咽管瘤多见于5~15岁儿童及青少年,少数病例可发生于45~60岁成人。这种亚型由CTNNB1基因(编码 β -连环蛋白)的体细胞突变驱动,激活Wnt信号通路,通常表现为囊性肿瘤。相较于乳头型颅咽管瘤,造釉细胞型颅咽管瘤具有更高的

复发风险和不良预后,主要原因在于肿瘤与下丘脑、垂体柄等周围重要结构紧密粘连并呈浸润性生长,限制了手术的完全切除^[2]。乳头型颅咽管瘤多由体细胞 BRAF V600E 突变引起,主要发生于成人,发病高峰为 40~50 岁,通常表现为实性肿瘤。临床上,颅咽管瘤患者常出现头痛(颅内压增高引起)、视觉障碍、电解质紊乱、中枢性尿崩症及体温调节异常等症状。颅咽管瘤患者长期生存率较高,但因肿瘤紧邻下丘脑、垂体和视交叉,易引发下丘脑损伤、内分泌功能障碍及视觉障碍等并发症,严重影响患者生活质量。此外,因下丘脑-垂体功能障碍,颅咽管瘤患者可继发代谢紊乱,增加代谢相关脂肪性肝病(metabolic dysfunction-associated fatty liver disease, MAFLD)等肝脏疾病的发生风险,具体机制见图 1。

1 流行病学

MAFLD 是在排除酒精及其他明确肝损伤因素后,以肝脂肪变性为共同特征的一组疾病。代谢相关脂肪性肝是指肝细胞内脂质蓄积而没有其他相关病理特征,这是 MAFLD 的最早期阶段。代谢相关脂肪性肝炎(metabolic dysfunction-associated steatohepatitis, MASH)是指肝细胞内脂质蓄积并伴有炎症和肝细胞损伤,随着炎症持续,肝纤维化逐渐进展。若 MASH 持续进展而未进行治疗,最终可能发展为肝硬化及其并发症,如肝肺综合征(hepatopulmonary syndrome, HPS)。颅咽管瘤患者由于肿瘤紧邻下丘脑、垂体和视交叉,常因下丘脑损伤和内分泌功能障碍而并发 MAFLD。约 50% 存在下丘脑受累的颅咽管瘤患者并发 MAFLD,通过近红外光谱测量的体脂量是一个有效的预测因素^[3]。在儿童期发病的颅

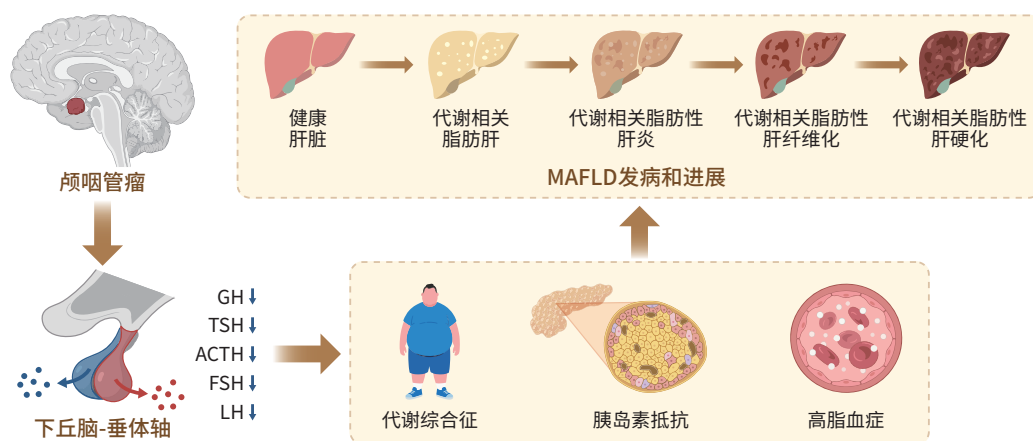
咽管瘤患者中,下丘脑性肥胖(hypothalamic obesity, HO)是 MAFLD 的重要危险因素,其总患病率约为 46.8%,而在肝转氨酶 ≥ 40 U/L 的儿童期发病颅咽管瘤患者中,MAFLD 的患病率更是高达 68.8%^[4]。两篇病例报告分别描述了 1 例 19 岁和 1 例 15 岁的颅咽管瘤患者均在手术后出现 MAFLD,并进展为 HPS^[5-6]。上述病例报告和研究结果表明,颅咽管瘤患者容易发生 MAFLD、肝硬化甚至 HPS,但这一临床现象易被神经外科、内分泌科及消化科医生忽视,从而降低了患者的生存期及生活质量。

2 颅咽管瘤相关肝脏疾病的病因

2.1 HO

手术切除后放疗仍被认为是颅咽管瘤治疗的金标准。在手术治疗中,全切手术虽可降低颅咽管瘤的复发率,但会增加下丘脑损伤的风险;而次全切除术虽能降低下丘脑损伤的风险,但会增加复发率。肿瘤本身、外科手术或放疗均会损伤下丘脑,引起儿童期发病的颅咽管瘤长期幸存者出现严重的 HO,导致代谢综合征和心脑血管疾病的发生率增加,降低患者的总生存期和生活质量。研究显示,与一般人群相比,颅咽管瘤患者的代谢综合征患病率更高^[7]。30%~70% 的颅咽管瘤患者在手术后会发展为 HO,因此,避免不可逆的下丘脑损伤是治疗颅咽管瘤的关键^[8-9]。HO 是颅咽管瘤相关代谢及肝脏并发症的核心病理环节,其发生涉及复杂的神经内分泌与行为调节机制,是连接下丘脑损伤与后续代谢异常、肝脂肪变性的关键桥梁。

2.1.1 能量调节中枢功能障碍 下丘脑的室旁核、弓状核、腹内侧核和后部(背内侧核和下丘脑背侧区),是能



注:GH,生长激素;TSH,促甲状腺激素;ACTH,促肾上腺皮质激素;FSH,卵泡刺激素;LH,黄体生成素;MAFLD,代谢相关脂肪性肝病。

图1 颅咽管瘤患者发生MAFLD的机制图

Figure 1 Diagram illustrating the mechanism of MAFLD in craniopharyngioma patients

量平衡调节的关键部位,这些部位的结构损伤通常会导致患者食欲亢进、中枢胰岛素和瘦素抵抗。生理状态下,瘦素作用于下丘脑弓状核,诱导厌食、产热,促使机体处于分解代谢状态,导致体重减轻。而瘦素抵抗则导致贪食、肥胖和继发性胰岛素抵抗,上述改变共同促进肝脂肪变性的发生。此外,瘦素抵抗还可以促进脂肪细胞产生肿瘤坏死因子 α (一种与肝纤维化相关的信号蛋白^[10])、自主神经张力改变(具体表现为交感神经活动减少、迷走神经张力增加)、能量消耗减少和脂肪组织中能量储存增加,其共同结果使患者体重迅速增加^[11]。

2.1.2 神经内分泌与行为调节异常 (1)昼夜节律紊乱:丘脑的视交叉上核是哺乳动物脑内最重要的昼夜节律起搏器,位于视交叉上方,其受损后可导致昼夜节律和睡眠-觉醒周期异常。视交叉上核调节夜间松果体褪黑激素的分泌,人体血液循环中的褪黑激素主要来源于此。儿童期发作的颅咽管瘤患者夜间褪黑激素水平显著降低,与白日嗜睡和昼夜节律紊乱有关^[12]。因此,颅咽管瘤患者出现白日嗜睡和昼夜节律紊乱,可能会因白日身体活动减少间接引起能量消耗减少和体重增加。(2)奖赏与进食行为改变:下丘脑外侧区的下丘脑-中皮质边缘回路参与食欲与饱腹感的调节^[13]。此外,视交叉上核内的多巴胺释放水平与进食行为有关,影响体重调控。(3)神经肽信号受损:催产素是一种下丘脑分泌的激素,可通过减少能量摄入、增加能量消耗、促进肌肉和骨骼合成、增加脂肪分解等途径促进体重减轻。颅咽管瘤患者可能在下丘脑催产素信号传导的异常或受损^[14]。

一项横断面研究中纳入29例下丘脑损伤的颅咽管瘤患者为研究组,31例无功能性垂体腺瘤患者作为对照组,发现下丘脑损伤患者的术后体重增加发生率显著高于对照组,且下丘脑损伤可通过改变大脑反应、注意力、饱腹感和饮食行为等机制导致体重增加^[15]。越来越多的研究发现,颅咽管瘤患者的下丘脑损伤会通过多种机制导致获得性HO。此外,术前体重指数(body mass index, BMI)被认为是术后发生HO的独立危险因素,术前BMI较高的患者术后发生HO的风险更高^[16]。

2.2 垂体功能障碍 下丘脑室旁核含有调节多种垂体激素的关键激素,对下丘脑室旁核的损害以及对垂体的直接损害均会导致垂体功能不全,生长激素、甲状腺激素、睾酮和雌激素是重要的代谢激素。54%~100%的颅咽管瘤患者存在垂体激素缺乏^[17],通常是由肿瘤本身或是经过治疗后下丘脑-垂体轴功能紊乱所引起,最常见的激素改变是生长激素缺乏,且多为永久性缺乏,可在

88%~100%的病例中观察到,也常出现促性腺激素缺乏(80%~95%)、促甲状腺激素缺乏(39%~95%)和促肾上腺皮质激素缺乏(55%~88%)。垂体功能减退可能是快速进展性MAFLD的罕见原因^[18]。一项横断面研究调查了76例儿童期发作的垂体功能减退患者和74例年龄、BMI匹配的对照组,发现垂体功能减退症患者的MAFLD患病率显著高于对照组^[19]。希恩综合征是指产时或产后发生大出血甚至失血性休克,引起垂体动脉痉挛、闭塞,垂体血液供应减少或中断,引起垂体前叶组织细胞变性坏死,从而导致垂体功能减退的临床综合征。在对一组希恩综合征患者进行平均(9.8±6.8)年的随访后发现,63%的患者存在MAFLD,显著高于同年龄段的普通人群,且其中有51%的患者存在严重的脂肪变性^[20]。甲状腺激素缺乏可通过引起高脂血症促进MAFLD的发生发展^[21]。性激素缺乏与葡萄糖、脂质代谢紊乱有关,从而触发MAFLD发生的分子通路^[22]。雌激素水平降低会导致血脂异常及肝脏脂肪堆积,与绝经前女性相比,男性和绝经后女性患代谢综合征及MAFLD的风险更高^[23]。垂体功能减退通常伴有泌乳素水平和泌乳素受体基因表达水平降低,泌乳素通过其特异性肝脏受体发挥作用,并下调分化抗原36水平,从而减少肝脏甘油三酯蓄积,降低脂质含量并防止肝脂肪变性。一项纳入456例MAFLD受试者的研究中,MAFLD组患者的循环泌乳素水平显著低于无MAFLD对照组^[24]。

2.3 生长激素缺乏 生长激素促进线性生长的作用已为学界所熟知,然而临床上较少关注到其代谢特性。肝脏是生长激素的重要靶器官之一,生长激素在肝脏中的生理作用包括抑制脂肪从头合成和促进脂质 β 氧化^[25]。近期研究表明,生长激素在抑制炎症反应以促进肝脏再生方面也发挥重要作用^[26]。生长激素作用于肝脏细胞,诱导其产生胰岛素样生长因子1(insulin-like growth factor-1, IGF-1),IGF-1的生理作用包括抑制炎症和纤维化通路,这些通路在肝脂肪变性向脂肪性肝炎和肝纤维化进展过程中发挥重要作用。总体而言,生长激素/IGF-1既可以直接作用于肝细胞以抑制脂肪变性和肝损伤,也可直接诱导肝星状细胞衰老以减缓纤维化进展,并作用于肝巨噬细胞使其从M1型(炎症型)向M2型(抗炎/促修复型)转变^[27]。

MAFLD与生长激素之间存在关联,生长激素缺乏患者罹患MAFLD的风险更高,其MAFLD患病率显著高于普通人群^[28]。相较于不合并生长激素缺乏的垂体功能障碍患者,合并生长激素缺乏的垂体功能障碍患者的

MAFLD患病率更高。一项纳入278例无功能垂体腺瘤患者的研究调查显示,生长激素缺乏症患者的MAFLD患病率是无生长激素缺乏症患者的2倍^[29]。生长激素受体-Janus激酶2-信号转导与转录激活因子5信号通路在MAFLD的发病机制中发挥重要作用。在生长激素受体肝脏特异性缺失的小鼠、肝脏特异性Janus激酶2缺陷小鼠以及信号转导与转录激活因子5缺陷小鼠中,均观察到肝脂肪变性的发生。IGF-1缺乏在脂肪肝形成中也至关重要,IGF-1可增强胰岛素敏感性,减少肝细胞中甘油三酯的蓄积^[30]。肝脂肪变性、肝纤维化与较低的IGF-1水平密切相关,表明生长激素缺乏会促进MAFLD的发生。

3 颅咽管瘤相关肝脏疾病的治疗

3.1 饮食运动控制 一项荟萃分析发现,西方饮食模式可使MAFLD的风险增加56%,表明饮食模式与MAFLD的发生密切相关^[31]。饮食控制和运动可逆转与MAFLD相关的脂肪变性、炎症和纤维化:提高全身胰岛素敏感性,并减少促进脂肪变性的代谢底物^[32],同时减少高脂饮食诱导的脂滴形成,降低肝脏中甘油三酯水平。运动和饮食干预分别通过激活腺苷一磷酸活化蛋白激酶/unc-51样自噬激活激酶1通路,以及抑制蛋白激酶B/哺乳动物雷帕霉素靶蛋白/unc-51样自噬激活激酶1通路,增强脂肪吞噬,从而改善MAFLD。此外,运动可促进肌肉分泌成纤维细胞生长因子21,其通过肝脏中的腺苷一磷酸活化蛋白激酶依赖性通路介导脂肪吞噬,从而改善MAFLD^[33]。通过改变生活方式减轻体重可改善肝脂肪变性,即使未实现体重减轻,运动也可以减少肝脂肪变性,并降低丙氨酸氨基转移酶和天冬氨酸氨基转移酶水平^[34-35]。因此,对于这类患者,应重视饮食及运动管理。

3.2 HO的管理 颅咽管瘤手术后下丘脑损伤的发生率为95%,其中术前即存在下丘脑损伤表现的患者占35%^[36]。因此,避免手术中下丘脑损伤所带来的HO是预防MAFLD发生的重要措施之一,但目前颅咽管瘤的最佳治疗方法尚未最终确定,需通过更保守的手术方法联合新型放疗方式,以降低治疗后HO的发生率。近年来,立体定向放射外科手术和放射增强剂等先进治疗方式的探索,有望改变这些病变的管理格局。Ganau等^[37]强调了立体定向放射外科的精确靶向能力,可实现最佳肿瘤控制,同时最大限度地减少对周围健康组织的损伤。目前尚无获批用于治疗HO的药物,一项纳入12例患者的回顾性研究显示,标准剂量的哌醋甲酯能够改善BMI^[38]。拟交感神经药物芬特明与另一种药物托吡酯

的组合已被批准用于治疗12岁及以上患者的一般肥胖症^[39],但其对HO的疗效尚不明确。其他拟交感神经药物如咖啡因和麻黄碱,在包含3例患者的病例报告中显示出一定疗效^[40]。特索芬辛是一种单胺再摄取抑制剂,原先用于治疗帕金森病和阿尔茨海默病,因其抑制食欲进而使体重减轻的副作用,使其具有作为减肥药物的潜力^[41]。然而,上述药物的数据多来源于结果各异的小型研究,尚未在HO患者中开展更新和更有效的临床试验,部分药物因血栓栓塞等重大不良事件或其他安全问题已被停用。胰高血糖素样肽1受体激动剂、催产素、蛋氨酸氨肽酶抑制剂和选择性黑皮质素4受体激动剂Setmelanotide等药物可能成为HO的新型治疗选择,但其疗效尚需未来研究进一步验证^[42-46]。

3.3 垂体激素的替代治疗 临床上发现,多数颅咽管瘤患者仅接受了必要的生命激素(如糖皮质激素、甲状腺激素)的替代治疗,而忽视生长激素的个体化替代治疗;但并非所有成年颅咽管瘤患者均需进行生长激素替代,需结合患者的生长激素缺乏状态、合并症及获益风险比综合判断。早期生长激素治疗对于改善颅咽管瘤并发MAFLD患者的预后具有重要意义。一项研究将24例年龄在18~29岁、BMI ≥ 30 kg/m²、质子磁共振波谱测定的肝脂肪分数 $\geq 5\%$ 、IGF-1 Z评分 ≤ 0 分的年轻受试者随机分为重组人生长激素治疗组与未治疗组,结果显示重组人生长激素治疗可降低肝脏脂肪含量,但仍需更大规模研究以证实该结论^[47]。一例13岁女童在接受颅咽管瘤手术4年后出现活动耐力下降、严重发绀、胸闷和喘息,肝胆超声、肝活组织检查和右心造影剂超声心动图显示肝硬化和多种垂体激素缺乏,提示HPS,在接受重组人生长激素治疗1年后,其肝功能和氧合状态均得到显著改善^[48]。Nishizawa等^[49]招募了69例生长激素缺乏的垂体功能减退患者,这些患者均接受除生长激素以外的其他垂体激素替代治疗,其中77%患有MAFLD,而年龄、性别和BMI匹配的对照组MAFLD患病率为12%;与对照组相比,生长激素缺乏症患者的血清丙氨酸氨基转移酶、天冬氨酸氨基转移酶、甘油三酯和胰岛素抵抗指数均更高;16例患者接受了肝活组织检查,14例存在MASH证据,其中5例MASH患者接受了6~12个月的生长激素替代治疗,并重复接受肝活组织检查和生化评估,与治疗前相比,生长激素疗法显著降低了MASH患者的血清肝酶浓度,并改善了肝脏的组织学变化,同时纤维化标志物浓度亦降低。因此,对于这类患者,应重视垂体激素的替代治疗。

4 小结与展望

颅咽管瘤是MAFLD的罕见病因之一,其病因复杂,包括HO、垂体功能障碍及生长激素缺乏等。临床医师需充分重视颅咽管瘤患者易继发MAFLD这一问题,方能实现早期诊断和及时治疗。目前颅咽管瘤的最佳治疗方法尚未最终确定,因此需采用更保守的手术方法联合新型放疗方式,以降低介入后下丘脑损伤的发生率,进而降低HO和MAFLD的发生率。对于颅咽管瘤患者MAFLD的治疗,应以生活方式干预为基石,药物和减肥疗法为手段,同时重视垂体激素的替代治疗,尤其是生长激素的替代治疗。

展望未来,应进一步深入探讨下丘脑损伤在代谢综合征及MAFLD发生中的具体作用机制,以此为新药研发提供潜在靶点,从而为实现更精准、有效的临床防治开辟新前景。

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