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黄韧带骨化危险因素研究进展

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摘　要

黄韧带骨化(ossification of the ligamentum flavum, OLF)是导致胸腰椎椎管狭窄的重要病因，以往由胸腰椎黄韧带骨化所致胸腰椎椎管狭窄的病例并不多见。然而，随着中国居民健康意识及影像学技术的发展，黄韧带骨化所致椎管狭窄的病例越来越多的被发现。黄韧带骨化可合并硬脊膜粘连，因而增加相关手术风险及术后并发症的可能。梳理阐明黄韧带骨化的危险因素，对认识此种疾病并拓展新的诊疗思路至关重要，故本文对韧带骨化的高危因素进行综述。

关键词

黄韧带骨化，致病机制，Osx，炎症，骨质疏松症

Research Progress on Risk Factors of Ossification of Ligamentum Flavum

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Abstract

Ossification of the ligamentum flavum is an important cause of thoracolumbar spinal stenosis. In the past, the cases of thoracolumbar spinal stenosis caused by ossification of the ligamentum flavum were rare. However, with the development of Chinese residents' health awareness and imag-

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ing technology, more and more cases of spinal stenosis caused by ossification of the ligamentum flavum have been found. Ossification of the ligamentum flavum can be associated with dural adhesions, thus increasing the risk of surgery and the possibility of postoperative complications. It is very important to clarify the risk factors of ligamentum flavum ossification for understanding this disease and developing new diagnosis and treatment ideas, so this paper summarizes the high risk factors of ligamentum flavum ossification.

Keywords

Ossification of Ligamentum Flavum, Pathogenesis, Osx, Inflammation, Osteoporosis

1. 引言

OLF 属于脊柱韧带病理性异位骨化性疾病，颈椎、胸椎和腰椎均可发生，其中最常发生在胸椎，尤其是以下胸段最为常见(T9~T12)，且胸段脊髓受压的危害最大，疾病的预后最差[1]。目前，国内外有关于OLF发病率的流行病学统计尚不多见，但有数据表明，在中国南方汉族人口中的发病率约为3.8% [2] [3] [4]。后路椎板切除椎管减压术是常规治疗 OLF 所致的椎管狭窄症的方法；然而，由于黄韧带骨化病灶常其与硬脊膜粘连，在分离椎板时易造成脑脊液漏，故手术过程具有挑战性[1] [5]，并且有较多高风险的围手术期并发症[6] [7]。因此，寻找与胸椎 OLF 相关的危险因素有助于提高对该疾病的发病机制的认识，进而拓展新的诊疗方向。本文将逐一对这些危险因素进行阐述。

2. 常见危险因素

2.1. 遗传

Runx2 是参与成骨细胞骨化过程所的关键因子。Runx2 可调节成骨细胞骨化，促进骨组织生成和重建，同时促进多能干细胞向软骨细胞分化。基因分型显示 Runx2 中两个位点 RS1321075 和 RS12333172 在 OLF 患者和对照组之间存在差异，其中一个单倍型位点被证明与 OLF 的发病率存在联系[8]。Osterix 是成骨细胞分化和骨硬化的重要转录因子。骨髓蛋白基因 Bsp 是骨和牙齿的矿化过程中起重要作用的一种蛋白质。研究人员发现，Osx 的缺失会导致 Bsp 表达的消失，通过实验，研究人员发现过表达 Osx 可以激活 Bsp 的表达，从而揭示了 Osx 对 Bsp 基因的直接调控作用[9]。Notch 是介导细胞信号转导的受体蛋白，影响成骨细胞增殖、分化和骨化[10] Runx2 和 Osterix 的表达在黄韧带细胞成骨分化过程中以与 Notch 2 的方式相似，将 Notch 2 敲低和过表达影响其表达水平。Notch 信号在 OLF 中起重要作用，Notch 可能通过与 Runx 2 和 Osterix 相互作用影响黄韧带细胞的成骨分化[11]。值得一提的是，通过全基因组分析，Osterix 被证实和骨折疏松这一种以骨丢失的代谢性疾病有关[12]，验证此两种疾病的相关性或许会为认识黄韧带骨化的发病机制提供新的思路。[13] [14]

2.2. 代谢紊乱

因此，弥漫性特发性骨肥厚、佩吉特病、氟中毒、腺癌转移、低磷血症维生素 D 抵抗性佝偻病、羟磷灰石和钙代谢紊乱可能导致 OLF [15] [16]。有研究表明骨骼氟含量超标可引起 OLF [17]。Kumar H 等

人的实验发现氟化物可能通过刺激已发生退变的黄韧带细胞向成骨细胞分化、成熟，而且在诱导黄韧带退变基础上进一步骨化[18] [19]。

2.3. 机械应力

Yin Zhao [20]等研究发现对大鼠黄韧带施加周期性张应力可诱发 OLF，持续时间越长，成骨作用越明显。CD 44、骨形态发生蛋白 2 (BMP-2)、整合素 b3、I 型胶原蛋白 1 (COL 1)、骨桥蛋白(OPN)、侏儒相关转录因子 2 (RUNX-2)和血管内皮生长因子(VEGF)的蛋白和 mRNA 表达成骨相关分子在 3 个实验组中的表达均增加，即成骨相关分子的上调和协同作用可能参与了张应力诱导的 OLF。Kim 等[21]研究脊髓 von-Mises 应力和横截面积对脊髓压迫的不同程度和形状的影响，发现当脊髓横截面积减少 30%~40%或压缩 4 mm 发生形变时，会出现脊髓症状。虽然关于机械应力的研究相对较多，但仍无法解释所有病例的致病机制，在欧美、非洲等地关于机械应力导致 OLF 的报道较少。胸椎的运动受到限制。推测的机制如下。当张力增加时，黄韧带中的 BMP-2、TGF-β 和 SOX 升高。然后，成纤维细胞分化成成软骨细胞和成骨细胞，最后向韧带骨化发展[22]。它在东亚更频繁地发展的原因之一被认为是由于这些地区人群习惯上更频繁地采取蹲位[23] [24]。但是脊柱局部应力的异常所造成的影响对解释 OLF 致病机制有其局限性。

2.4. 炎症

在最近的研究中，炎症在新骨形成过程中所起到的作用越来越被学者们所重视。在骨折发生后，机体会激活 TNF-α 炎症信号通路，TNF-α 介导软骨细胞凋亡和控制破骨细胞对软骨内组织重塑的促吸收细胞因子的表达。虽然 TNF-α 受体消融后的动物其骨骼并没有明显的发育改变，但结果说明了 TNF-α 功能在促进创伤后骨折修复中起主要作用，并表明骨骼组织发育和出生后修复的过程部分由不同的机制控制。此过程对骨组织的重建至关重要。[25] [26] Zhao Yongzhao 等认为，高全身免疫炎症指数和体重指数是胸椎黄韧带骨化症的独立危险因素

2.5. 年龄、性别、BMI

有研究表明，年龄、是否吸烟、患者 BMI 指数是 TOLF 发生的临床危险因素，吸烟可能影响 OLF 的病情进展及严重程度，而 BMI 指数过高可能会诱导新发 OLF，这一点在胸椎的 OLF 中尤其重要，年龄被证明是是 TOLF 的危险因素，但在女性患者组中的统计学结果表明其不能作为女性 OLF 患者的独立危险因素[27] [28] [29]。

3. 总结

综上所述，对于 OLF 的致病机制及相关危险因素，近年来国内外学者们做了很多的探索，也提出诸多关于 OLF 致病机制的假设，如本文所提到的代谢紊乱、机械应力、年龄、性别、BMI 等，故 OLF 很可能是由多因素参与共同导致的。最值得关注的是，有研究表明 TNF-α 通路在 OLF 中参与骨化过程，而对此过程的进一步研究可能进一步解释 OLF 的病因，进而更加充分地认识此疾病以拓宽诊疗思路及研发新的药物。

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