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Научный обзор

Нейрогенная гетеротопическая оссификация. Обзор литературы. Часть первая

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АННОТАЦИЯ

Обоснование. Гетеротопическая оссификация — это образование костной ткани в мягких тканях организма. Отдельной формой гетеротопической оссификации является нейрогенная, то есть возникающая в результате тяжелого повреждения головного или спинного мозга различного генеза. Нейрогенная гетеротопическая оссификация — сложный многофакторный процесс формирования дифференцированной кости в параартикулярных мягких тканях крупных суставах. Гетеротопическая оссификация приводит к формированию стойких контрактур и анкилозов, обусловливающих тяжелую инвалидизацию и затрудняющих реабилитацию этих пациентов.

Цель — проанализировать публикации по различным аспектам нейрогенной гетеротопической оссификации.

Материалы и методы. В первой части обзора представлен анализ литературы, посвященной эпидемиологии, факторам риска формирования, патогенеза, клинической картины и лабораторной диагностики нейрогенной гетеротопической оссификации. Поиск данных осуществляли в базах научной литературы PubMed, Google Scholar, Cochrane Library, Crossref, eLibrary без языковых ограничений. Глубина поиска составила 30 лет. В процессе написания статьи использовали метод анализа и синтеза информации.

Результаты. Изложены современные литературные данные по проблеме гетеротопической оссификации у пациентов с патологией центральной нервной системы. Освещены актуальные вопросы этиологии, факторов риска, патогенеза, клинической картины и лабораторной диагностики данного патологического процесса.

Заключение. Понимание факторов риска развития нейрогенной гетеротопической оссификации и их профилактика в контексте современных знаний о патогенезе этой патологии может способствовать снижению частоты формирования гетеротопической оссификации у пациентов с тяжелым повреждением центральной нервной системы.

Ключевые слова: нейрогенная гетеротопическая оссификация; гетеротопический остеогенез; травма спинного мозга; черепно-мозговая травма.

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Review

Neurogenic heterotopic ossification: A review. Part 1

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ABSTRACT

BACKGROUND: Heterotopic ossification is the formation of bone tissues in the soft tissues of the body. A distinct form of heterotopic ossification is neurogenic, that is, resulting from severe injury to the brain or spinal cord of different genesis. Neurogenic heterotopic ossification is a complex multifactorial process of differentiated bone formation in the paraarticular soft tissues of large joints. Heterotopic ossification leads to the formation of persistent contractures and ankylosis, which cause severe disability and complicate rehabilitation.

AIM: To analyze publications dealing with various aspects of neurogenic heterotopic ossification.

MATERIALS AND METHODS: In the first part of our review, we present the results of the literature analysis on the epidemiology, risk factors, pathogenesis, and clinic and laboratory diagnosis of neurogenic heterotopic ossification. Scientific literature databases PubMed, Google Scholar, Cochrane Library, Crossref, and eLibrary were searched for without language limitations.

RESULTS: Current literature data on heterotopic ossification in patients with central nervous system pathologies are presented. Topical questions of etiology, risk factors, pathogenesis, and clinic and laboratory diagnostics of this pathological process are highlighted.

CONCLUSIONS: Understanding the risk factors of heterotopic ossification development and their prevention in the context of the modern knowledge of heterotopic ossification pathogenesis may help reduce the incidence of heterotopic ossification in patients with severe central nervous system injury.

Keywords: neurogenic heterotopic ossification; heterotopic osteogenesis; spinal cord injury; cerebral trauma.

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科学审查

神经源性异位骨化。文献综述。第一部分

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简评

论证。异位骨化是指在人体软组织中形成骨组织。异位骨化的另一种形式是神经源性骨化，它是由于各种原因造成的严重脑损伤或脊髓损伤而发生的。神经源性异位骨化是大关节旁软组织中分化骨形成的一个复杂的多因素过程。异位骨化导致持续性挛缩和强直的形成，造成严重残疾，并使这些患者的康复变得复杂。

目的。本研究旨在分析有关神经源性异位骨化各个方面的出版物。

材料和方法。综述的第一部分分析了有关神经源性异位骨化的流行病学、形成风险因素、发病机制、临床表现和实验室诊断的文献。数据在科学文献数据库PubMed、Google Scholar、Cochrane Library、Crossref和eLibrary中进行搜索，无语言限制。搜索深度为30年。在撰写文章的过程中采用了信息分析和综合的方法。

结果。本文介绍了有关中枢神经系统病变患者异位骨化问题的现代文献资料。内容涉及这一病理过程的病因、风险因素、发病机制、临床表现和实验室诊断等当前问题。

结论。了解神经源性异位骨化发病的风险因素，并结合现代发病机理的相关知识加以预防，可能有助于降低严重中枢神经系统损伤患者异位骨化形成的频率。

关键词：神经源性异位骨化；异位成骨；脊髓损伤；颅脑创伤。

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论证

异位骨化（heterotopic ossification，异位骨化）是一种在骨骼外形成分化骨组织的病理过程，即在与最初确定的骨骼间质没有连续性连接的地方形成骨组织[1]。

Reidel于1883年首次描述了创伤后异位骨化的形成过程。第一次世界大战期间，A. Dejerne、A. Ceiller和A. Dejerine-Klumpke对脊髓损伤脊髓损伤士兵中异位骨化的形成进行了研究[2]。

异位骨化既可能是遗传性疾病（如进行性骨化性纤维发育不良）的临床表现，也可能是创伤和烧伤导致的后天性疾病[3]。在血肿组织、原发性结核病灶、术后疤痕、大血管和心脏瓣膜的动脉粥样硬化钙化灶、不同组织发生的肿瘤、脊柱的韧带装置以及韧带附着区域的骨骼其他部位，都有发生异位骨化的病例[4，5]。另一种异位骨化是神经源性异位骨化，即由于各种原因造成的严重脑损伤或脊髓损伤（严重颅脑外伤、脊髓损伤脊髓损伤、脑卒中、脑缺氧）而引起的异位骨化[6]。

目的。本研究旨在分析有关神经源性异位骨化各个方面的出版物。

材料和方法

综述的第一部分介绍了有关神经源性异位骨化的流行病学、形成风险因素、发病机制、临床表现和实验室诊断的文献分析结果。数据在PubMed、Google Scholar、Cochrane Library、Crossref和eLibrary数据库中进行搜索，无语言限制。搜索深度为30年。在撰写文章的过程中，我们采用了信息分析与综合的方法。

结果与讨论

流行病学和风险因素

在严重脑外伤患者中，神经源性异位骨化的发生率为10%至23%，在脊髓损伤患者中为10%至53%[7，8]，在爆炸伤后高达65%[9，10]。根据J.E. Reznik等人对413名患者（262名脑外伤患者和151名脊髓损伤患者）的治疗结果进行了分析，发现脊髓损伤术后神经源性异位骨化（neurogenic heterotopic ossification，神经源性异位骨化）的发生率高于脑外伤术后。因此，在有严重颅脑创伤后遗症的患者中，有3.9%的病例被诊断出神经源性异位骨化，而在脊髓损伤患者中，有10.6%的病例被检测出神经源性异位骨化[11]。

关于神经源性异位骨化血型的性别发病率，文献给出了非常矛盾的观点：男性是女性的2.5倍[12，13]，女性是男性的4倍[14]。根据对小鼠异位骨化的实验建模数据，雄性小鼠异位骨的形成比雌性小鼠多30%，作者认为这是由于雄性小鼠体内胰岛素样生长因子-1和骨形态发生蛋白（BMP）的水平增加所致[15]。

世界文献中有关神经源性异位骨化发病率的年龄特异性数据比性别特异性数据更为一致。神经源性异位骨化多在20-30岁发现，儿童发病率低于成人，主要在10岁及以上[7，16，17]。根据文献记载，最早发现神经源性异位骨化的儿童只有5岁[16]。在儿科患者中，神经源性异位骨化的发病率与性别没有明显的相关性[16，17]。

A. Estraneo等人对278名不同病因的脑损伤患者的检查和治疗结果进行了回顾性分析，结果显示，创伤性脑损伤患者（19.3%）比缺氧性脑损伤患者（10.7%）和血管性脑损伤患者（6.4%）更容易形成神经源性异位骨化[13]。在脑外伤患者中，弥漫性轴索损伤患者更常观察到神经源性异位骨化[14]。据报道，在脑损伤后处于植物人状态的患者中，神经源性异位骨化的发生率是短期意识障碍患者的2倍[17]。

M. Citak等人认为，脊髓完全中断是脊髓损伤患者形成神经源性异位骨化的主要诱因[18]。脊髓损伤的部位也会影响神经源性异位骨化形成的发生率。例如，颈椎和胸椎水平的损伤比腰椎水平的损伤患神经源性异位骨化的风险更高[19]。

除了脊髓或脑损伤这一直接事实外，还发现了其他导致神经源性异位骨化的风险因素：胸部外伤、气管切开术、尼古丁使用、肺炎和尿路感染[18，20]。

许多学者[13、15、18]认为，人工通气也是创伤后和脊髓损伤后发生神经源性异位骨化的风险因素。这是因为在某些情况下，长时间人工通气会导致呼吸性碱中毒，而正是这种碱中毒促成了神经源性异位骨化的形成[21]。

H. Krauss等人称高凝状态是脊髓损伤患者发生神经源性异位骨化的另一个危险因素[22]。这一理论与J.Reznik等人的数据相一致，他们将深静脉血栓纳入了外伤后遗症和脊髓损伤患者发生神经源性异位骨化的附加风险因素[11]。然而，Y. Yolcu等人参考了他们关于神经源性异位骨化发生风险因素的补充分析和系统文献综述的数据，指出脊髓损伤后遗症患者的深静脉血栓形成与神经源性异位骨化风险之间没有相关性[20]。

根据N. Rawat等人认为，褥疮会导致局部炎症过程的发展，这可能是脊髓损伤患者神经源性异位骨化形成的触发机制[23]。不过，也有一些学者认为，并非所有脊髓损伤背景下的压疮患者都会发展成神经源性异位骨化[18，24]。

不同作者对肌肉痉挛作为神经源性异位骨化风险因素的看法也不一致。一些学者仍然认为痉挛是一个危险因素[19，20]，而另一些学者则不同意[2]。大多数脑瘫患者都会出现痉挛，但在目前的国内外文献中，我们没有发现既往未接受过手术治疗或无外伤史的此类患者出现过神经源性异位骨化。

尽管在一项回顾性研究中，G. Orchard等人指出他们研究的唯一与神经源性异位骨化形成显著相关的风险因素是卧床时间[26]，但固定不动作为神经源性异位骨化风险因素的作用仍在研究之中[25-27]。一方面，我们可以将这些数据解释为缺乏运动与神经源性异位骨化的形成直接相关。另一方面，卧床休息的时间长短取决于神经源性异位骨化形成的其他因素，如脑和脊髓损伤的严重程度、骨和软组织创伤，卧床休息时间长会增加压疮的风险并促进慢性炎症的发展。因此，目前还不能明确地将缺乏运动与神经源性异位骨化形成的发生率相提并论。

发病机制

目前，人们认为神经源性异位骨化是由软骨内骨化形成的，但也有一些学者认为异位骨化是由膜内骨化形成的[3，28]。K. Foley等人在对90份神经源性和非神经源性异位骨化组织学制备样本（18名患者）的研究中发现，异位骨化是由软骨内骨化形成的。作者还描述了异位骨化形成的六个连续阶段：血管周围淋巴细胞浸润阶段、淋巴细胞迁移到软组织阶段、反应性纤维增生阶段、新血管生成阶段、软骨形成阶段和软骨骨形成阶段。同时，正如作者自己指出的那样，他们不能完全排除膜内骨化形成异位骨化的可能性，但鉴于缺乏所有组织学制备中膜内骨化的数据，这种可能性极低[29]。

据长期观察，合并中枢神经系统创伤的患者骨折处骨茧形成和完全固结的时间明显短于无神经系统病变的患者。这一观察结果已在实验和临床研究中得到证实[30，31]。严重的脑外伤和脊髓损伤会导致神经元、神经胶质细胞和血管受损，从而引发一连串复杂的细胞和分子变化，这些变化可能会导致从受伤那一刻开始的进一步损伤。此类损伤的常见继发性损伤机制可能包括兴奋毒性（神经递质能够过度激活NMDA和AMPA受体，从而导致神经细胞损伤和死亡的过程）、离子失衡、氧化应激、缺血、水肿和神经炎症（中枢神经系统神经元分泌的细胞因子和趋化因子介导的一个过程、中枢神经系统胶质细胞、内皮细胞和外周免疫细胞分泌的细胞因子、趋化因子介导的过程[32]。神经炎症会导致血脑屏障、血椎屏障和血神经屏障受损[33]，并为神经肽的异常循环创造条件，尤其是P物质和降钙素基因相关肽，它们会导致血管扩张，增加血管通透性，并为炎症介质和生长因子的外周迁移创造条件，从而可能刺激神经源性异位骨化的形成[32-34]。O. Gautschi和他的合著者设法在实验室中证实了这一假设。体外研究表明，脑外伤患者体内的血清和酒精会促进成骨细胞的增殖[35]。

F. Genêt等人的实验证明，免疫炎症反应是形成神经源性异位骨化的一个必要因素。作者假设，神经源性异位骨化的形成需要肌肉组织同时受到损伤，并使用肌肉损伤和修复的通用模型对此进行了模拟。在不同基因系的小鼠身上重复了该实验，结果类似。现已证实，这不是一种遗传易感现象[36]，中枢神经系统结构损伤和软组织损伤在神经源性异位骨化的发病中起着重要作用[34，37]。这一发现与矿井爆炸造成脑、脊髓和四肢软组织严重受损后神经源性异位骨化高发病率的数据相关[38]。

然而，没有软组织创伤史的中风后遗症患者会形成神经源性异位骨化[39]。根据D. Alexander等人的研究，在各种原因导致的中枢神经系统损伤患者中，感染性炎症过程（尿路感染、褥疮、气管插管、肺炎）被认为是神经源性异位骨化发生的危险因素，是细胞因子产生和免疫系统激活的触发机制，为异位骨化的形成提供了基础[37]。一些学者认为，全身炎症和细胞因子风暴可能会导致新发严重冠状病毒感染患者出现异位骨化[40，41]。

淋巴细胞、巨噬细胞和肥大细胞会释放细胞因子和生长因子，包括白细胞介素-1β、白细胞介素-6、oncostatin M、神经营养素-3、激活素A、骨形态发生蛋白、转化生长因子β等，从而启动参与神经源性异位骨化形成的细胞分化[3，42]。形成异位骨化的主要细胞来源是骨骼肌和筋膜结缔组织中间质来源的局部基质或成纤维细胞，以及循环干细胞和祖细胞[1，3]。

外周神经也是参与神经源性异位骨化形成的细胞来源[33]。在异位骨化诱导后，从神经周膜和神经内膜提取的细胞中发现了成骨细胞特异性转录因子的表达[43]。当血神经屏障的完整性被破坏时，这些细胞就会从周围神经的内膜和外膜区域迁移到形成异位骨化的区域，并进一步分化为成骨细胞、软骨细胞和棕色脂肪细胞[44]。

根据TIE2、PDGFRα、SCA1、GLAST、FSP1、STRO1、GLI1和MX1的表达，确定了实验动物中可能参与异位骨化形成的细胞。然而，在人类体内，这些细胞类型尚未得到准确描述。有人认为，其他类型的细胞可能是导致人类发生异位骨化的原因[45]。例如，对于内皮细胞参与神经源性异位骨化的形成，研究人员尚未达成共识。根据D. Medici及其合著者的研究，内皮细胞中活性ALK2的表达会导致内皮-间充质转化和干细胞样表型的获得，从而使细胞具有成骨分化能力[46]。然而，进一步的研究并未证实内皮细胞参与了特异性神经源性异位骨化的形成，尽管在实验性烧伤和创伤模型中已证实内皮细胞对异位骨化的形成有贡献[47]。

之前的大量研究表明，BMP/SMAD和WNT/β-catenin等多种信号通路参与了异位骨化的调控[24，27，48]。

BMPs是TGFβ超家族的成员。典型的TGFβ/BMP信号是一个线性级联，涉及TGFβ/BMP配体、两种类型的受体（I型和II型）以及信号转换器SMAD。受体与BMP结合后，通过SMAD 1/5/8途径进行信号转导，TGFβ则导致SMAD2/3磷酸化。活化的SMAD与SMAD4结合，然后复合物聚集在细胞核中，在那里调节目标基因的表达。例如，这些通路的一个下游靶点是编码RUNX2的基因，RUNX2是众所周知的骨生成主调节因子，在骨化软组织中也有异常表达[49，50]。依赖于TGFβ的SMAD2/3激活可在早期阶段促进成骨细胞的迁移和分化，同时抑制成骨的后续阶段。不涉及SMAD的TGFβ依赖性途径可通过TAB1-TAK1复合物导致MAPK p38或MAPK ERK1/2途径的激活，从而诱导RUNX2激活并促进破骨细胞分化[51]。BMPs和TGFβ可激活不依赖于SMAD的途径。大多数BMP配体都是通过SMAD依赖性和SMAD非依赖性信号通路诱导成骨转录因子发挥作用的强效骨剂[52，53]。

依赖于TGFβ的SMAD2/3激活在早期阶段促进成骨祖细胞的迁移和分化，但同时在晚期阶段抑制成骨[54]。在胚胎和出生后的发育过程中，TGFβ/BMP信号与其他途径相互作用，这一点已得到公认。例如，有人描述了典型WNT通路、TLR通路或mTOR通路之间的交叉对话。值得注意的是，在异位骨化的早期阶段，mTOR可调节缺氧和炎症信号，而在后期阶段，相同的通路对软骨生成和成骨至关重要[52]。利用渐进性骨化性纤维软骨病的小鼠模型证明了mTOR通路信号的增加[55]。

低氧环境会稳定低氧诱导因子1α（HIF1α），而低氧诱导因子1α可调节许多参与异位骨化形成的蛋白质（如血管内皮生长因子或BMP）的产生[42]。对三种不同的骨化性纤维发育不良小鼠模型的分析表明，在缺氧条件下，HIF1α信号增强[56]。在严重烧伤患者的脂肪组织样本中，HIF1α的表达也有所增加[56，57]。

然而，对于未携带任何基因突变的患者来说，异位骨化的发病机制仍不清楚。此外，即使在晚期骨化性纤维软骨发育症患者中，也并不总是能在软组织中观察到异位骨化，似乎是创伤和机体炎症反应的结果，这有力地说明了免疫炎症反应与异位骨化之间的联系。

因此，体内实验研究表明，将细菌移植到实验动物的胫骨中可增加骨胼胝体的体积。在同一项研究中，脂联素（一种源自细菌细胞壁的TLR2激活因子）被确定为一种骨刺激因子[58]。

这些研究数据表明，异位骨化形成的主要机制与TGFβ/BMP通路信号有关，后者会导致成骨转录因子的表达。受损组织中存在的因子会导致mTOR、WNT或TLR通路的激活，它们既可以与TGFβ/BMP相互作用，也可以独立发挥作用，即促进成骨因子的表达并诱导异位骨化的形成[27]。

临床表现

神经源性异位骨化形成于髋关节（60.9%）、膝关节（14.3%）、肘关节（21.3%）和肩关节（35%）的关节旁，限制了受累关节的活动范围，直至完全强直，导致严重的疼痛综合征、神经和血管压迫[8，59]。

我们没有发现一例关节内 神经源性异位骨化病例。因此我们得出结论，神经源性异位骨化总是关节外的。关节囊也总是被保留下来。肌腱附着点可作为临床和器械检查的标志。静脉受到压迫，关节周围动脉的直径通常没有变化。一些患者可能会出现受影响关节的滑囊炎，这是形成的异位骨化对关节旁组织造成损伤的反应[2]。

在脊髓损伤患者中，神经源性异位骨化通常在脊髓损伤水平的尾部被发现，髋关节最常受到影响。根据D. Garland等人的数据，这类患者的髋关节受累占所有有临床意义的神经源性异位骨化的97%[7]。

严重外伤的后果会导致髋关节、膝关节、肘关节或肩关节等关节周围结构受累的全身性异位骨化[60]。在40%的此类患者中，病变过程只累及一个关节[28]。在超过2/3的病例中，神经源性异位骨化位于髋关节的关节旁组织或股骨周围的软组织中。约90%的脑外伤患者合并肘关节内骨折或脱位，在受伤关节区域出现异位骨化，而无严重脑外伤的患者肘关节临床显著异位骨化的发生率为3%至6%[14]。

根据T. Ebinger等人的研究，神经源性异位骨化的病因可能会影响其在髋关节的位置。例如，在严重的脊髓损伤患者中，55%的神经源性异位骨化病例位于大腿前表面，而在脑卒中或脑外伤患者中，40%的病例位于前内侧表面。据报道，32%的重度脑缺氧患者的神经源性异位骨化位于大腿后表面[61]。H. Ko认为，在脊髓损伤后遗症中，髋关节神经源性异位骨化更有可能位于后内侧和前内侧。作者认为，这是由于髋关节内收肌出现静力所致[62]。D. Garland在描述严重创伤后遗症患者髋关节后内侧主要形成神经源性异位骨化组织时也给出了同样的论据[7]。神经源性异位骨化通常位于髂前上棘和股骨之间[61]。

踝关节和腕关节以及手脚小关节的神经源性异位骨化病例极为罕见[6，7]。

神经源性异位骨化的形成时间如下：最常见的情况是在脊髓损伤后第3周至第12周之间出现[8]。根据R. Wittenberg等人的研究，脊髓损伤后5个月是神经源性异位骨化风险最高的时期[63]。临床表现取决于病程的不同阶段。病程分为四个阶段：急性、亚急性、慢性未成熟异位骨化和慢性成熟异位骨化[64]。

在急性期（持续约2周），异位骨化形成区域会出现致密的水肿，通常是高渗性水肿。肿胀位于关节周围，会严重限制关节的活动。在这一阶段，临床表现类似于下肢静脉血栓形成，这导致诊断错误频发，尤其是在无法进行超声血管诊断，且医生未意识到这种症状的其他可能原因时[65]。脊髓损伤后的患者在出现神经源性异位骨化临床表现时，由于这类创伤特有的感觉缺失，可能不会伴有主观感觉。这些患者体温升高，肌肉痉挛。如果神经源性异位骨化较小，其形成可能不会引起局部反应，如高血压、局部发热和水肿。这种大小的异位骨化很少导致四肢关节挛缩，因此不会影响生活质量[15]。

在亚急性期（持续时间为2至8周），局部炎症过程的迹象会消退，受影响关节的活动会受到限制[8]。异位骨化在软组织中形成，体积增大，并与邻近骨结构的骨膜融合[2]。

在未成熟异位骨化的慢性期（病程6-8个月），受影响的关节部位会触及形状不规则的致密肿块。关节的运动幅度减小[3]。

骨组织的骨化成熟在6-18个月内完成。成熟的异位骨化在组织学和放射学上与正常骨组织相似，由带有哈弗氏管的管状骨、皮质层、血管和带有一定程度造血功能的骨髓组成[45]。

在成熟期异位骨化的慢性阶段（病程8-18个月），可能会出现关节强直。在这一阶段，在受累关节区域触诊到的病理形态已具有骨密度特征[15]。一些学者指出，关节强直是在未成熟异位骨化阶段形成的[28，61]。

实验室诊断

非特异性炎症指标（CRP）可用于监测疾病的活动性。非特异性炎症指标水平的正常化与异位骨化炎症阶段的消退相关[62]。J. Wilkinson和I. Stockley认为，体温升高与非特异性炎症指标和肌酸激酶活性水平升高相结合，应被视为异位骨化发展的迹象[66]。

碱性磷酸酶（ALP）是一种敏感但非特异性的异位骨化指标。在异位骨化形成过程中，碱性磷酸酶水平会明显升高。但是，一旦骨化生长停止，酶的水平就会下降并恢复正常，因此不能用于诊断异位骨化[67]。碱性磷酸酶水平平均在异位骨化首次出现临床症状前7周开始升高，并在临床表现出现前3周达到峰值。从这个时候开始，碱性磷酸酶水平逐渐下降，并在5个月左右达到正常水平。碱性磷酸酶水平的升高程度与异位骨化的大小直接相关。大量骨形成可能会导致碱性磷酸酶水平长期升高，而轻微的异位骨化可能不会伴随着该指数的变化[28]。根据G. Kluger的研究，在大多数情况下，儿科患者的碱性磷酸酶值不会升高[16]。因此，碱性磷酸酶水平的正常化并不能证明神经源性异位骨化生长过程的稳定和停止。然而，迄今为止，碱性磷酸酶水平测定是早期神经源性异位骨化与其他炎症过程鉴别诊断中唯一可广泛使用的方法，因为该指标在神经源性异位骨化生长活跃期明显增加，而在炎症过程中变化不大[67]。

实验室诊断的前景

microRNA的调控紊乱可能在异位骨化的发生发展中起着重要作用。例如，肱骨骨折患者体内microRNA-421水平的降低与BMP2的过度表达和异位骨化的高发病率有关[68]。今后，microRNA水平的变化或许可被视为神经源性异位骨化发生的可能指标。

与几乎健康的人和没有神经源性异位骨化的脊髓损伤患者相比，异位骨化的发展特点是骨形成显著增加。L. Edsberg和合著者对非遗传性异位骨化患者和无异位骨化的对照组患者（全髋关节置换术后）血清中的蛋白质组概况进行了比较分析，结果表明，在异位骨化患者组中，骨钙素前蛋白、骨调制蛋白前体和前蛋白异构体2链alpha-1 (v)胶原的生成量在统计学上显著增加。这些蛋白质可被视为异位骨化的潜在临床生物标记物[69]。V. Povoroznyu和合著者认为，骨钙素水平≥49.6 ng/ml和1型胶原蛋白N末端前肽水平≥187.3 ng/ml应被视为脊髓损伤后遗症患者神经源性异位骨化发育的标志物，这些标志物可被纳入诊断算法[67]。对骨重塑标志物的进一步研究将有助于早期诊断和预测结果，并有可能预防神经源性异位骨化的发展。

结论

神经源性异位骨化是大关节旁软组织骨形成的一种复杂的多因素过程，会导致严重残疾，并使因各种原因造成的中枢神经系统损伤后遗症患者的康复工作复杂化。根据有关神经源性异位骨化发病机制的现代知识，了解神经源性异位骨化的风险因素及其预防措施，以及对骨重塑的监测，可能有助于降低严重中枢神经系统损伤后遗症患者异位骨化的形成频率。

其他信息

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