

# 郎格汉斯组织细胞增多症的消化系表现、诊断及治疗

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## Digestive system manifestations, diagnosis and treatment of Langerhans cell histiocytosis

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## Abstract

Langerhans cell histiocytosis (LCH) is a rare disease characterized by an abnormal proliferation of histiocytes, known as Langerhans cells (LCs). At present, the pathogenesis of LCH remains unknown. LCH often involves the bone, skin, lung, bone marrow and lymph nodes. Besides, the liver, bile duct and gastrointestinal tract may also be affected. LCH has no specific clinical manifestations compared to other digestive system diseases. Once digestive system involvement is diagnosed in LCH patients, prompt treatment (even liver transplantation) should be given. In this paper, we will review the digestive system manifestations, diagnosis and treatment of LCH.

**Key Words:** Langerhans cell histiocytosis; Gastrointestinal tract; Clinical manifestation; Therapy

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## 摘要

郎格汉斯组织细胞增多症是一种少见的全身多系统受侵犯的组织细胞异常增生性疾病, 常见受累部位为骨、皮肤、肺脏、骨髓、淋巴结等, 除此之外, 尚可侵犯肝脏、胆道及胃肠道等消化器官, 临床表现与其他消化系统疾病相比缺乏特异性, 故诊断难度较大. 一旦郎格汉斯组织细胞增多症患者明确诊断消化系统受累, 则需要系统性治疗, 甚至是肝脏移植. 本文综述郎格汉斯组织细胞增多症的消化系统表现, 从而对其早期诊断及治疗提供帮助.

**关键词:** 郎格汉斯细胞性组织细胞增多症; 消化系统; 临床表现; 治疗

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## 0 引言

郎格汉斯细胞性组织细胞增多症(langerhans cell histiocytosis, LCH)是一组病因未明的组织细胞(单核巨噬细胞系统和树突状细胞系统)增殖性疾病, 因1868年Paul Langerhans最早在表皮组织中描述而得名. 本病为少见疾病, 好发于婴儿和儿童, 成人尤为罕见<sup>[1-3]</sup>. 最近, 法国的1项流行病学调查结果表明, 该病年发病率为4.6/100万儿童(0-14岁)<sup>[4]</sup>, 而在成年人中的发病率仅为1/100万-2/100万<sup>[5]</sup>. LCH可侵犯1个或多个器官和组织, 骨骼系统较为多见, 亦可侵犯如皮肤、肺脏、下丘脑、垂体、淋巴结、肝脏和脾脏等<sup>[6-16]</sup>. 其病因和发病机制尚未明确, 近年来研究发现多与体内免疫调节紊乱有关<sup>[17-24]</sup>. 其病程可呈迅速进展致死, 也可缓慢进展. 研究显示, 其临床进展、治疗的效果及预后与郎格汉斯细胞(langerhans cells, LCs)侵犯的部位有关<sup>[25]</sup>. LCH临床表现各异, 消化系统脏器中肝脏、胆道、胃肠道等均可受累, 可为唯一受累器官, 也可多系统LCH受累部位之一, 并可能为多系统LCH患者的首发症状. 成人LCH患者通常因为其主要症状而就诊于不同的专科门诊, 这就为

## ■背景资料

郎格汉斯组织细胞增多症隶属组织细胞疾病范畴, 国际组织细胞学会为国际上研究此疾病的最权威机构. 在我国, 郎格汉斯组织细胞增多症患者多于血液科治疗, 但因其浸润器官的多样性, 消化科医生也可能首诊此类患者. 因此, 消化科医生有必要掌握郎格汉斯组织细胞增多症的临床特点及其消化系统表现.

## ■同行评议者

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## ■研究前沿

目前国内外学者普遍认为郎格汉斯组织细胞增多症可以侵犯多种消化器官,并且与疾病预后相关。但因郎格汉斯组织细胞增多症属少见疾病,尤其在成人中更为罕见,目前发表的文章多为个案报道,其典型的消化系统临床表现仍无系统总结。

其疾病的明确诊断带来了很大的困难。因此,消化科医生应该充分认识LCH的消化系统表现,有助于患者尤其是成年患者的早期诊断、选择恰当的治疗方案及其正确判断预后。为此,本文将对LCH的消化系统表现、诊断和治疗进行综述。

## 1 LCH的消化系统表现

1.1 肝脏 LCH是一种临床表现多样的疾病,可仅表现为无需或仅需微小干预治疗的孤立皮疹或者单纯的骨溶解,也可浸润到内脏器官,如肝脏、脾脏,引起肝、脾肿大。肝脏受累较为常见,肿大程度不一,大多为轻至中度肿大<sup>[26]</sup>。

肝脏可为LCH患者唯一的受累部位,也可作为多器官损害之一。典型的多器官LCH患者肝脏受侵犯的比例为20%,脾脏30%,淋巴结为50%。因此,当患者出现肝脾肿大,同时伴有淋巴结肿大时,应警惕LCH的可能。无症状性的肝脏肿大、黄疸、生化异常,如转氨酶升高、高胆红素血症和/或凝血酶原时间延长,提示肝脏LCH的存在<sup>[27]</sup>。目前,组织细胞学会提出的对于肝脏受累的诊断标准为:肝肿大,锁骨中线肋缘下>3 cm和/或肝功能异常(如排除其他原因所致的低蛋白血症<55 g/L,低白蛋白血症<25 g/L)和/或肝脏组织病理学诊断。这一诊断标准被临床工作者广泛接受并应用于临床。在组织学上,肝脏病变可分为4个病理分期,即增殖期、肉芽肿期、黄瘤期和纤维化期。受LCs浸润的肝脏可表现为3种不同的病理学形态,一为汇管区的炎症细胞浸润,炎症细胞主要由淋巴细胞构成,同时伴有数目不等中性粒细胞和嗜酸细胞<sup>[26]</sup>;二为汇管区被S-100染色阳性的LC浸润,并沿胆管规则排列,为LCH最常见的组织学表现<sup>[28]</sup>;三为与组织细胞浸润相关的汇管区纤维化。影像学能够显现病理活检漏诊的病变,对于疾病分级和评估肝脏受累的程度具有重要意义。在影像学上,肝脏病变与疾病的4个病理分期相关。在增殖期和肉芽肿期,汇管区有LC浸润、炎症和水肿,在超声上表现为汇管区低回声,CT上为低回声,注入对比剂后可增强<sup>[29]</sup>。MRI T1-W像低信号、T2-W像高信号<sup>[29,30]</sup>。黄瘤期门脉周围的脂肪浸润在超声上表现为高回声,而在CT上仍为低密度结节,MRI则为T1-W像高信号、T2-W像低信号<sup>[29,31]</sup>。在纤维化期组织学上表现为管周纤维化和由硬化性胆管炎引起的结节性胆汁性肝硬化,超声上表现边界清晰的汇管区低回声病灶,有局灶性钙化。胆管造影和磁共振胰胆管水成像

见胆管扩张,可呈串珠状<sup>[29,32]</sup>。

1.2 胆道 LC可浸润胆管系统,引起胆管的组织学改变<sup>[33]</sup>。典型的病理改变为硬化性胆管炎(sclerosing cholangitis, SC),表现为胆管弥漫性炎症、广泛纤维化增厚和胆管狭窄。多发生于治疗无效的病情活动的LCH患者及既往有LCH病史而无病情活动迹象的患者<sup>[34-36]</sup>。SC可发生于小胆管和大胆管甚至是胆总管,可表现为不规则的胆管狭窄和/或扩张,胆管壁钙化增厚,在成人可合并胆管结石,最终可发展为肝硬化。LCH是儿童SC的主要原因之一,大约有<sup>[33]</sup>的儿童SC继发于LCH。在成人中,仅有部分病例报道,尚无系统统计。

1.3 胃肠道 胃肠道功能紊乱在LCH患者中很常见,但是有关胃肠道LCs浸润的证据很少。只有在内镜活检阳性时,才能够明确胃肠道受累的诊断。胃肠道受累常见部位为食管、胃、十二指肠、直肠乙状结肠及回盲部。内镜下胃及十二指肠多表现为多发浅溃疡形成,可伴有黏膜下出血;结肠镜下除多发浅溃疡形成外,尚可见结肠和末端回肠的结节性增生及管腔狭窄<sup>[37]</sup>。此外,尚有成人LCH仅表现为孤立的结肠息肉而无其他器官受累的报道<sup>[38]</sup>。

Hait等<sup>[39]</sup>检索了从1966-2004年Medline发表的英文文献,关键词为“Langerhans cell histiocytosis”“colitis”和“gastrointestinal tract”。共检索到明确诊断胃肠道受累的LCH病例报道22例。分析发现,其主要症状为便血(59%)、无血性腹泻(18%)、肛周瘘管(4%)和便秘(9%)。便血仅发生在多器官受累的LCH患者,77%的患者同时合并低蛋白血症。86%(12/14)行胃镜检查的患者存在十二指肠LCH的组织学证据,其中8例存在下消化系症状(便血,腹泻)。上消化系活检阳性率高(100%),而下消化系活检阳性率仅为64%。

## 2 诊断

LCH的诊断依靠典型的临床表现和病理组织学以及免疫组织化学结果,确定诊断要靠病理组织学的典型镜下表现(且S-100a免疫染色阳性或电镜下Birbeck颗粒阳性)<sup>[40-42]</sup>。LCH主要的病理改变为病变组织中存在数量不等的组织细胞,即郎格汉斯细胞,此细胞在光镜下为单个核细胞,平均直径12 μm,胞质中等量质匀,有细小的粉红色颗粒,少见有胞质空泡和吞噬现象。胞核常有折叠或切迹(核沟),或呈多叶状,核染色质

不规则, 含有1-3个嗜碱性的核仁融合的组织细胞, 偶可形成多核巨细胞. 有丝分裂相缺如病变组织内尚可见少量嗜酸性粒细胞、淋巴细胞、浆细胞和中性粒细胞. 在透射电镜下LCH胞质内含有一种特殊的细胞器, 朗格汉斯细胞颗粒或称Birbeck颗粒, 其功能尚未明了, 这种Birbeck颗粒为LCs所特有.

### 3 治疗

2008年国际组织细胞学会发表了LCH的推荐意见<sup>[40]</sup>指出, LCH侵犯器官的发生率与患者的年龄相关, 通常情况下, 儿童多见单病灶或多病灶的骨损害, 成人则单病灶的肺脏损害多见. 并提出了LCH疾病严重程度的临床分层, 将其分为单器官系统疾病(single organ system disease)和多器官疾病(multi-organ disease), 前者包括单病灶(unifocal)和多病灶(multifocal), 后者又分为无器官功能障碍(no organ dysfunction)和器官功能障碍(organ dysfunction). 器官功能障碍依据受累的器官又可分为低风险(侵犯皮肤、骨、淋巴结、脑垂体)和高风险(侵犯肺脏、肝脏、脾脏、造血系统). 并根据此临床分层选择相应的治疗方案<sup>[43]</sup>.

通常情况下, 单器官单病灶的LCH需要最小的治疗, 如单病灶骨病变仅需要局部活检刮除<sup>[44-46]</sup>. 如果没有合并器官功能障碍, 也可以采取等待的方案, 给病灶自愈的时间及机会. 多系统多病灶的LCH需要系统治疗, 系统治疗可以降低患者的死亡率和复发率<sup>[47-55]</sup>. 2009年公布的LCH III治疗指南是目前对LCH患者治疗方案选择的最权威意见, 指南中包括对各种临床分层的儿童LCH患者的推荐治疗方案<sup>[56]</sup>.

LCH与肝脏疾病的关系包括急性LCH导致的肝脏病变和LCH的肝脏后遗症, 鉴于两者治疗不同, 要严格区分以上两种情况. 急性LCH肝脏受累患者的死亡率是不受累患者的3倍, 大约有65%的患者经过化疗后肝脏病变可以消退, 35%的患者肝脏病变会持续进展<sup>[53]</sup>. 急性硬化性胆管炎的儿童在诊断后立即行肝脏移植, 不发生移植后复发或者对化疗敏感者预后较好, 可不进一步发展为慢性肝病和终末期肝硬化<sup>[57]</sup>.

LCH导致的终末期肝病和急性LCH肝脏受累且对化疗不敏感患者也需要进行肝移植, 其长期存活率约为80%, 但很多患者移植后出现急性排斥反应, 部分对激素治疗无效者需行再次肝移植<sup>[58]</sup>. 虽然肝脏移植后LCH的肝外复发并不

少见, 但是肝内复发的病例很少见, 直到最近才有相关报道<sup>[59]</sup>.

目前报道胃肠道受累的LCH病例预后极差, 18 mo内的死亡率为59%, 化疗后完全缓解率仅为18%<sup>[39]</sup>. 因明确诊断胃肠道受累的LCH患者报道例数极少, 缺乏治疗经验, 原则上多器官多部位受累患者需进行系统治疗.

### 4 结论

LCH是一组少见的组织细胞增殖性疾病, 其发病机制尚未明确, 其临床表现各异, 多器官多部位均可受累, 因此增加了临床的诊断难度. 目前对儿童LCH的系统性研究较多, 其治疗方案也日渐成熟; 但对于成人LCH, 仅有少量病例报道, 仍缺乏相应的治疗指南. 国际组织细胞学会一直致力于成人及儿童LCH诊断及治疗的基础及临床试验的研究. 2009-04, 国际组织细胞学会批准了LCH的评价和治疗指南, 为临床LCH的治疗提供了新的有力的武器.

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### ■应用要点

本文通过对郎格汉斯组织细胞增多症的疾病特点及消化系统表现的详尽描述, 对此疾病的早期诊断及预后评估起到了积极的作用.



# 同行评价

本文就郎格汉斯组织细胞增多症在消化系统的临床表现、发病机制和临床表现做了综述,对于早期识别和治疗这种罕见的疾病有一定的参考价值。

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