Advances in Clinical Medicine 临床医学进展, 2023, 13(10), 16797-16806
Published Online October 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.13102352

Hans汉斯

转氨酶明显升高的病因及诊治

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收稿日期：2023年9月25日；录用日期：2023年10月19日；发布日期：2023年10月24日

摘　要

肝功能检查已经是各个医院常规的血液生化检查，其中天冬氨酸氨基转移酶(AST)、丙氨酸氨基转移酶(ALT)水平异常通常提示有肝细胞的损伤，需要进一步检查明确病因，其病因对死亡率有显著影响，氨基转移酶水平明显升高是临床工作中常见的问题，明确氨基转移酶重度升高的病因是临床工作中的一大难题，我们主要概述了可能导致氨基转移酶重度升高的各种病因及诊治。

关键词

氨基转移酶，急性肝损伤，病因，诊断，治疗

Etiology and Diagnosis and Treatment of Markedly Elevated Transaminases

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Received: Sep. 25th, 2023; accepted: Oct. 19th, 2023; published: Oct. 24th, 2023

Abstract

Liver function tests have been routine blood biochemical tests in various hospitals, in which abnormal levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are usually indicative of hepatocellular damage and require further investigation to clarify the etiology of the disease, which can have a significant impact on mortality, and a markedly elevated level of aminotransferase is a common problem in the clinical workup. Defining the etiology of severely elevated aminotransferases is a major challenge in the clinical workup, and we focus on outlining the vari-

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文章引用: 谢晓月, 俞慧宏. 转氨酶明显升高的病因及诊治[J]. 临床医学进展, 2023, 13(10): 16797-16806.
DOI: 10.12677/acm.2023.13102352

ous etiological factors that may lead to severe elevation of aminotransferases and the diagnosis and management of the disease.

Keywords

Aminotransferase, Acute Liver Injury, Etiology, Diagnosis, Treatment

1. 氨基转移酶

氨基转移酶是肝脏疾病最常见的测量指标，ALT 在葡萄糖和氨基酸的中间代谢中起着关键作用，AST 是调节谷氨酸水平的关键酶，在发育过程中参与肝脏葡萄糖的合成，并参与脂肪细胞的糖原异生[1]。两者在肝脏中均有较高的表达，AST 还广泛存在于心脏、骨骼肌、肾脏、大脑、胰腺、肺脏、白细胞、红细胞中，与之相反，ALT 在其他组织中浓度较低。因此，肝脏损伤时，ALT 是比 AST 更具特异性的标志物[2] [3]。两者很可能通过肝脏、脾脏和骨髓中的巨噬细胞内吞作用而被清除[4] [5]，ALT 的半衰期约为 50 小时，AST 的半衰期约为 20 小时[6]。

氨基转移酶的正常血清水平在人群和个体中存在很大的变异，影响因素包括性别、年龄、种族、环境因素、昼夜变化和遗传因素等[7]。氨基转移酶实验室正常值定义为与平均值相差不超过 2 个标准差的取值范围，转氨酶升高的程度分为轻度[<5 × 正常上限(ULN)]、中度(>5 ~ <15 × ULN)和重度(> 15 × ULN) [8]，氨基转移酶重度升高常提示存在急性肝损伤，不同病因导致的急性肝损伤预后差异大，而且天冬氨酸氨基转移酶(AST)升高的峰值水平与患者死亡率呈正相关[9]明确病因是临床医生刻不容缓的工作，药物性肝损伤、病毒性肝炎、缺血性肝炎是引起急性肝损伤最常见的原因，少数肝豆状核变性(Wilson disease)、肝脏血管性疾病(布加综合征、遗传性出血性毛细血管扩张症(HHT)、静脉闭塞性疾病(VOD))、自身免疫性肝炎也可表现为急性肝损伤[10]，近年来越来越多的研究表明胆总管结石导致氨基转移酶重度升高，临床医生们应将其纳入鉴别诊断中，避免延误疾病的进一步治疗。

2. 氨基转移酶明显异常的最常见病因

2.1. 药物性肝损伤

药物性肝损伤被归类为直接性和特殊性。直接药物性肝损伤通常与剂量有关，发生在接触该药物的很大一部分人身上(可预测)，发病时间在短时间内(数小时到数天)，对乙酰氨基酚是导致直接药物肝损伤的主要原因，是最常用的非处方止痛药之一，它还广泛存在于安眠药、感冒药及其他非处方药物中，它通常是一种安全的药物，成人每天的治疗剂量为 4 g，但故意或无意的过量可导致严重的肝损伤，甚至急性肝功能衰竭[11]。特殊药物性肝损伤通常与药物剂量无关并表现出不同的发病潜伏期，抗生素是导致特殊药物性肝损伤的最常见药物类别[12]，近年来，人们对与草药制剂和膳食补充剂(HDS)等替代药物相关的潜在肝毒性的认识正在增加[13] [14]。现在新型免疫治疗药物，包括生物制剂，特别是针对晚期癌症的免疫抑制剂的使用，会造成肝损害在内的免疫介导的不良反应，这些治疗方法导致了新兴的药物性肝损伤形式，给医生带来了新的挑战[15]。

由于发病率相对较低、临床表型的多样性以及缺乏特异性的生物标志物，药物性肝损伤的诊断是肝病专家面临的最具挑战性的肝病之一[16]。对于宿主来说，年龄、性别、种族、饮酒、怀孕、慢性肝病是药物性肝损伤的危险因素[15]。药物性肝损伤患者大多数临床表现为急性的肝酶升高，伴黄疸或偶尔伴凝血功能障碍和脑病等，但缺乏明确的检测方法，肝脏组织学可以提供补充信息，并帮助确保准确诊断[17]，在转氨酶重度升高的病因中，肝活检主要用于区分药物性肝损伤和血清标志物无明显特异性的无症状自身免疫性肝炎，在一项包含 35 例药物性肝损伤和 28 例自身免疫性肝炎的小规模对比研究中，肝细胞胆汁淤积和门脉中性粒细胞提示药物性肝损伤，肝纤维化提示自身免疫性肝炎[18]。肝脏组织学同时也是判断药物性肝损伤预后的手段之一，组织学表现为肉芽肿、嗜酸性粒细胞浸润的药物性肝损伤通常有较高的生存率，组织学表现为中性粒细胞浸润、较高程度的坏死、较高程度的纤维化、胆小管的胆汁淤积、胆管反应、门静脉病变、小泡型脂肪变性提示预后极差，死亡率及肝移植的发生率高[19] [20] [21]。药物性肝损伤的治疗同样是临床一大难题，目前并没有特定的治疗方法，管理药物性肝损伤患者最重要的第一步是停用相关药物，当停用相关药物后，大多数药物性肝损伤患者可自发恢复，这也是药物性肝损伤诊断中的重要一环[22] [23]，当药物性肝损伤患者转氨酶明显升高发展为急性肝衰竭时主要治疗方法有两种：1) 在有毒药物到达肝脏之前，快速清除有毒药物以阻止进一步的攻击；2) 一旦药物到达肝脏，就使用一种解毒剂来防止和/或停止攻击性。活性炭可以在对乙酰氨基酚急性摄入后 3~4 小时内阻止药物的进一步吸收[24]，在发生急性肝衰竭过程中早期使用 n-乙酰半胱氨酸可以防止患者发展为更严重的脑病，也可发挥肾脏保护作用。当其他药物均不能产生作用时，通常会使用皮质类固醇。针对一些特征性的药物性肝损伤有特定药物的治疗，消胆胺可用于有胆汁淤积的药物性肝损伤，消胆胺是一种胆汁酸树脂，可以加快药物清除的速度[25]。肉碱是丙戊酸盐肝毒性的特异性解毒剂，动物模型和人类研究表明，及时给予肉碱(尤其是静脉给药时)可改善急性丙戊酸盐肝毒性的生存[26] [27] [28] [29]。但与药物治疗相比，肝移植仍然是药物性肝炎导致急性肝衰竭的主要抢救治疗方法，在患有急性肝衰竭的肝移植受者中，1 年生存率约为 80% [24]。

2.2. 病毒性肝炎

甲型、乙型、丙型、丁型、戊型肝炎均会导致转氨酶的升高。甲型肝炎和戊型肝炎通常引起急性肝炎，乙型肝炎和丁型肝炎可以是急性或慢性的，而丙型肝炎通常是慢性的。急性病毒性肝炎表现为转氨酶的明显异常，有时转氨酶大于 1000 U/L，而慢性肝炎的转氨酶通常为轻度异常或在正常范围内。甲型肝炎病毒是一种单链的、非包膜的核糖核酸(RNA)分子，主要通过人与人之间的接触或摄入受污染的食物或水传播[30] [31]，急性甲型病毒性肝炎可通过检测甲型肝炎免疫球蛋白 M (IgM)抗体来诊断，免疫球蛋白 G (IgG)抗体在感染后也会呈阳性，免疫球蛋白 M (IgM)抗体的滴度随着时间的推移而下降，并且在暴露 1 年后通常检测不到，但 IgG 抗体终身存在，并给予终身免疫[32]。大多数感染甲型病毒性肝炎的患者可自愈，治疗主要是预防性的，在可能接触之前接种疫苗，并在接触后接种疫苗和 HAV 免疫球蛋白，以提供主动免疫和被动免疫[33]。乙型肝炎病毒是一种脱氧核糖核酸病毒[34]，其诊断通常是通过乙型肝炎表面抗原(HBsAg)的存在及 HBV DNA 病毒载量来确诊，乙型肝炎表面抗体阳性提示接种过疫苗或既往感染。乙型病毒性肝炎很少表现为急性暴发性肝炎，确诊为急性乙型病毒性肝炎后需积极抗病毒治疗，现有的抗 HBV 的抗病毒药物是干扰素或核苷酸/核苷类逆转录酶抑制剂(NRTIs)，包括恩替卡韦、替诺福韦、拉米夫定、阿德福韦和替比夫定[35]。丁型肝炎病毒只能在乙肝病毒感染的宿主中复制，丁型肝炎的诊断最可靠的方法是通过逆转录酶－聚合酶链反应检测丁型肝炎 RNA [36]。丙型肝炎病毒是一种单链 RNA 病毒，主要通过血液传播[37] [38]，它的感染通常通过抗 HCV 抗体检测进行筛选，并用 HCV RNA 检测进行确认[39]，抗病毒是丙型病毒性肝炎的治疗方式。戊型肝炎病毒是一种单链、有包膜的核糖核酸

(RNA)分子[40]，主要通过粪口途径传播，它引起的戊型病毒性肝炎是急性、自限性疾病，可通过抗戊型肝炎病毒抗体(IgG/IgM)诊断，它可引起孕妇最常见的暴发性肝衰竭。目前预防戊型病毒性肝炎的疫苗在我国已批准使用[41]。

除了上述的五种肝炎病毒，一些疱疹病毒也会导致病毒性肝炎，据报道，8 种疱疹病毒可导致肝炎：单纯疱疹病毒 1 和 2、水痘带状疱疹病毒、巨细胞病毒、EB 病毒、人类疱疹病毒 6、7、8。单纯疱疹病毒性肝炎可发展为暴发性肝炎。早期给予大剂量静脉注射阿昔洛韦(5~10 mg/kg，每日 3 次)是治疗的关键[42]。

2.3. 缺血性肝炎

缺血性肝炎，也称为缺氧性肝炎或休克肝，是指没有任何已知急性肝炎原因的肝细胞损伤，其特征是转氨酶水平短暂升高(比正常值高 20 倍)，是在重症监护和术后环境中导致转氨酶显著异常的常见原因，也是转氨酶重度升高死亡率最高的病因，其住院死亡率高达 50%，韩国的一项多中心回顾性研究中，导致转氨酶水平显著升高的最常见疾病是缺血性肝炎(33.7%)，该组也是死亡率最高的(44.2%) [43]。美国的一项回顾性研究也证实了缺血性肝炎是导致肝衰竭的主要原因，而且通常与高死亡率相关[44]。

缺血性肝炎发生在急性和严重低血压的情况下，并与肝转氨酶(通常为>3000 IU/L)的突然显著升高相关，并在充分的循环灌注后的几天内恢复正常，所以早期诊断和及时的治疗至关重要。缺血性肝炎的诊断标准为：1) 具有心源性休克或呼吸衰竭等基础原发病；2) 血清氨基转移酶快速、显著的增高达正常值上限的 20 倍以上，并且具有可逆性，于 7~l0 d 内恢复至接近正常；3) 排除其他原因引起的肝细胞坏死，尤其是病毒性肝炎或药物性肝炎等[45] [46]。目前暂时缺乏治疗缺血性肝炎的药物，临床上主要以支持治疗为主。

3. 氨基转移酶明显异常的其他病因

3.1. 肝豆状核变性(Wilson Disease)

肝豆状核变性是一种由 ATP7B 突变引起的铜代谢常染色体隐性遗传病[47]。ATP7B 是一种铜转运蛋白，用于铜的胆汁排泄和功能性铜蓝蛋白合成，ATP7B 的功能异常导致铜在肝脏中过量蓄积，循环中大量非铜蓝蛋白结合的铜被摄取[48] [49]，导致铜在肝脏和大脑中的病理性积累[50]，从而导致神经精神变化和肝脏疾病，40%~60%的肝豆状核变性患者的第一临床症状是肝脏疾病[51]，5%病人表现为暴发性肝衰竭[52] [53]，暴发性肝衰竭最常见的临床症状是快速发作的黄疸、腹水、严重凝血功能障碍、急性肾功能衰竭和肝性脑病，与其他病因引起的急性肝衰竭类似。

肝豆状核变性患者临床症状缺乏特异性，其诊断需结合临床表现及实验室检查，铜蓝蛋白的降低(<20 mg/dL)、24 h 尿铜排泄量增加(>100 mg/24 小时) [54] [55]，肝脏活检肝脏铜浓度大于 250 mg/g 肝脏干重[56] [57]。当临床表现及实验室检查不能确诊时，可行 ATP7B 的直接基因测序，该基因测序也推荐用于肝豆状核变性患者主要亲属的家庭筛查，肝豆状核变性患者的 25%的兄弟姐妹可能发展为肝豆状核变性，0.5%~4%的肝豆状核变性患者的后代可能发展为肝豆状核变性[54] [58]。肝豆状核变性的治疗以脱铜治疗为主，根据不同的作用机制，治疗药物可分为铜螯合剂和锌盐，两者可促进多余的铜通过尿液或粪便排出。但当肝豆状核变性患者表现为暴发性肝衰竭时，肝移植是唯一有效的方法，并且预后也是令人满意的，根据两项随访研究，原位肝移植术后的 1 年生存率为 79%，最大生存时间为 20 年[59] [60]。但因为肝源有限，许多患者无法及时进行肝移植手术，肝细胞或干细胞移植是未来可能替代肝移植治疗肝豆状变性暴发性肝衰竭患者的有前途的治疗方法[61]。

3.2. 肝脏血管性疾病

布加综合征(BCS)是以肝静脉流出道梗阻为特征的疾病，梗阻部位发生在肝小静脉到下腔静脉(IVC)的交界处直至右心房[62]。根据梗阻病变的来源可以分为原发性或继发性布加综合征，原发性布加综合征定义为腔内静脉病变血栓形成导致静脉梗阻，继发性定义为临近结构如外源性压迫、肿瘤侵犯等造成的静脉梗阻[63]。布加综合征的临床表现各种各样，可以无症状，也可表现为暴发性肝衰竭[64] [65]，其最主要的临床三联征为腹痛、腹水和肝肿大，当患者表现为急性时，转氨酶可明显升高。多普勒超声检查是疾病诊断的关键，其灵敏度高达 75%以上[64]，超声诊断困难时，可采用 MR 成像及 CT 评估进行诊断确认[66]。确诊后患者应尽快行抗凝治疗，以减少原有血栓进一步进展和新发血栓的风险[67] [68]，严重者需要行血管成形术、溶栓、经颈静脉肝内门体分流术或手术减压合并门腔分流术[69]，失代偿肝硬化或急性肝衰竭患者需肝移植。

窦性梗阻综合征(SOS)，又称肝静脉闭塞性疾病(VOD)，其特征是肝血窦或肝内小静脉阻塞。与布加综合征相反，窦性梗阻综合征不是血栓性的，而是由于纤维闭塞的静脉内膜炎造成的，是造血肝细胞移植(HSCT)的一种罕见、可能危机生命的并发症[70]。患者通常在暴露后 1~3 周出现突然发作的右上象限疼痛、肝肿大、水肿和腹水，病情严重者可发展为器官衰竭，该病最常见的死亡原因是肝功能衰竭、肾功能衰竭、心肺功能衰竭。因缺乏特异性的生化指标及影像学表现，经颈静脉肝活检是首选的诊断方式[69]。该疾病主要以预防为主，对既往有肝病、正在行实体癌治疗等这些具有危险因素的患者降低骨髓抑制方案的强度或选择并发窦性梗阻综合征风险小的方案。治疗主要依赖对水钠潴留、败血症、器官衰竭的支持治疗，TIPS、外科分流术和肝移植已在个别病例中作为补救治疗得到了广泛的应用，需要更多的数据和前瞻性研究来自信地表明这种治疗方法在 SOS 中的价值。

3.3. 自身免疫性肝炎(AIH)

自身免疫性肝炎(AIH)是一种免疫介导的炎症性肝病，其免疫发病机制依赖于自身反应性 CD4 和 CD8 T 细胞，是在环境触发因素打破自身耐受后诱导的[71]。AIH 影响从儿童到老年人的各个年龄段的个体，但在中年女性中最常见[72] [73]。根据不同的临床表现，AIH 可以分为不同的亚型，其中急性起病的 AIH 是一种临床上具有挑战性的疾病亚型，因为延迟诊断和延迟治疗，特别是在缺乏典型血清学表现的情况下，可能导致较差的短期预后。2019 年 AASLD 实践指南和指南指出，在西方国家有 25%~75%的 AIH 患者表现为急性发病[71]，韩国的一项研究报告了 46.4%的 AIH 患者急性起病[74]，意大利的一项多中心队列研究中，将急性起病的 AIH 患者生化指标定义为转氨酶> 10 × 正常值上限(ULN)和胆红素> 5 mg/mL，报道共有 43%的 AIH 患者表现为急性起病[75]。

AIH 的诊断需要肝组织活检和生化指标的支持，1) 典型组织学：界面性肝炎，2) ALT、AST、免疫球蛋白 G (IgG)的升高，3) 自身抗体的异常，包括抗核抗体、抗平滑肌抗体、抗肝肾微粒体 1，4) 排除其他类似于 AIH 的肝脏疾病，包括病毒性肝炎、遗传性、代谢性、胆汁淤积性或药物性肝损伤(DILI)。AIH 治疗目的首先是缓解症状，然后实现生化反应，控制肝脏炎症向组织学缓解，预防疾病进展，促进纤维化的消退。单用皮质类固醇或低剂量皮质类固醇联合硫唑嘌呤(AZA)是 AIH 的一线治疗[76]，2019 年 AASLD 实践指南和指南更新了其推荐的一线治疗方案：泼尼松单药(40~60 mg/d)或泼尼松(20~40 mg/d)联合 AZA (50~100 mg/d)或布地奈德(9 mg/d)联合 AZA (50~100 mg/d) [71]。对于使用一线用药后没有达到完全的生化反应或不能耐受一线用药的患者则选择二线用药，其中吗替麦考酚酯联合泼尼松被证明是应用最广泛的二线用药方案，一项研究中表明吗替麦考酚酯联合泼尼松的治疗方案使 89%得到了组织学缓解[77]，一项对一线治疗失败患者的研究中也证实了二线治疗的有效性，生化缓解的诱导率达 60% [78]。

3.4. 胆总管结石

胆总管结石是临床上的常见疾病，通常表现为腹痛和肝生化指标的异常，包括碱性磷酸酶(ALP)、胆红素、转氨酶、胆汁酸的升高，根据传统的肝酶升高的模式，胆总管结石患者表现为胆汁淤积型，其中转氨酶表现为正常或轻至中度升高(<正常上限的 10 倍)，但近年来，越来越多的研究发现胆总管结石患者的转氨酶可表现为明显升高，一项研究收集了 740 例胆总管结石患者，其中有 209 例(28%)转氨酶水平明显升高(>正常上限的 10 倍) [79]，在多个转氨酶重度升高的病因研究中，胆总管结石这一病因均有一定的占比[9] [44] [80]。胆总管结石导致转氨酶重度升高的机制尚不明确，多个关于高转氨酶胆总管结石的研究表明，此类患者胆总管直径明显较小[79] [81] [82]，较窄的胆总管空间范围减少，结石梗阻导致胆道压力明显增加，胆汁回流到肝脏引起肝细胞损伤造成转氨酶显著升高[79]，在动物模型中，胆管结扎可以导致 AST 和 ALT 水平的升高[83] [84]也证实了这一猜想。此类患者受益于内镜胆道减压，当他们接受内镜下取石术后转氨酶可在短时间内下降并恢复正常值[79] [82]。与传统胆总管结石导致胆汁淤积型肝酶变化的观念相比，胆总管结石是转氨酶明显升高患者的重要鉴别诊断，需要早期识别，早期治疗，其预后效果佳，转氨酶水平通常可正常化。

4. 总结

转氨酶水平>400 U/L 提示存在肝细胞的损伤，不同病因导致肝细胞损伤的机制不同，从而会导致不同的预后，对病因的早期识别和诊治是关键。正如上述内容，导致转氨酶重度升高的原因很多，临床诊断困难，完整的病史、体格检查至关重要，同时也需要完善其他检验指标及影像学支持或确认诊断。虽然肝活检仍然是诊断的标准，但在肝脏严重受损期间再遭受有创性操作可能会加重病情，而且胆总管结石患者解除梗阻后转氨酶可达到正常化，需加强鉴别，避免有创操作，未来新的无创方式可能会取代肝活检。

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