

· 综述 ·

DOI: 10.12449/JCH250528

高胆汁酸血症的常见病因及诊断

李茂萍, 罗开忠

中南大学湘雅二医院感染科, 长沙 410011

通信作者: 罗开忠, luo_kz@csu.edu.cn (ORCID: 0000-0001-5643-7103)

摘要: 胆汁酸是胆汁的主要成分,是复杂的代谢调节剂和重要的信号分子,在脂肪代谢中发挥着关键作用。临床上高胆汁酸血症比较常见,但有时不易明确病因。本文综述了常见的引起高胆汁酸血症的疾病及其胆汁酸池组分的改变,以期为临床医生提供高胆汁酸血症的规范化诊断思路。

关键词: 高胆汁酸血症; 胆汁酸; 诊断

基金项目: 湖南省自然科学基金(2024JJ9150)

Common etiology and diagnosis of hyperbileacidemia

LI Maoping, LUO Kaizhong

Department of Infectious Diseases, The Second Xiangya Hospital of Central South University, Changsha 410011, China

Corresponding author: LUO Kaizhong, luo_kz@csu.edu.cn (ORCID: 0000-0001-5643-7103)

Abstract: Bile acids (BAs) are the main components of bile and serve as complex metabolic regulators and important signaling molecules, and they play a crucial role in fat metabolism. Hyperbileacidemia (HBA) is relatively common in clinical practice, but sometimes it is difficult to clarify its etiology. This article reviews the common diseases that cause HBA and the changes in the composition of the bile acid pool, so as to provide clear insights for the diagnosis of HBA.

Key words: Hyperbileacidemia; Bile Acids; Diagnosis

Research funding: Natural Science Foundation of Hunan Province (2024JJ9150)

1 胆汁酸代谢与高胆汁酸血症

胆汁酸是胆固醇经肝脏作用后的最终产物,是胆汁的主要成分。形成机制非常复杂,包括两种途径:经典途径(约占胆汁酸合成的75%)由胆固醇7 α -羟化酶催化,替代途径由27-羟化酶启动,主要产生初级胆汁酸:胆酸(cholic acid, CA)和鹅脱氧胆酸(chenodeoxycholic acid, CDCA)。CA和CDCA与甘氨酸或牛磺酸结合形成结合型胆汁酸^[1]。结合型胆汁酸经胆管进入肠道,在肠道菌群的作用下,转化为次级胆汁酸:脱氧胆酸(deoxycholic acid, DCA)和石胆酸(lithocholic acid, LCA)。人体内存在一个高效的胆汁酸保存和循环系统,称为肠肝循环,每天重复4~10次^[2-3]。

血清总胆汁酸(total bile acid, TBA)是肝功能检查的指

标之一,正常值范围在0~20 $\mu\text{mol/L}$ 。若是血清TBA值高于该参考值,即可诊断为高胆汁酸血症(hyperbileacidemia, HBA)。

2 常见的引起HBA的疾病

许多疾病都可能导致TBA升高,而其具体病因有时难以明确,且其治疗效果往往不佳。本文将对常见的引起HBA的疾病进行系统综述。

2.1 HBA与肝脏疾病

2.1.1 HBA与急慢性肝炎 健康人血清TBA水平极低,当肝细胞损伤或出现病变时,胆汁酸代谢会受到影响,导致进入血液的胆汁酸水平显著升高。故血清TBA的检测值可以作为判断肝实质损伤的一个重要指标^[4]。急性肝炎发病初期血清TBA浓度迅速升高并达到峰值,

当病情逐渐恢复时,TBA水平亦逐渐降低,几乎与谷草转氨酶同时恢复至正常水平。急性肝炎慢性化时,尽管转氨酶恢复正常,但大多数患者均有TBA升高。慢性活动性肝炎患者的血清TBA水平可轻度或中度升高^[5]。因此,TBA的测定及动态变化对急性和慢性肝炎的诊断以及病情转归判定有一定的指导意义。

2.1.2 HBA与肝硬化 肝硬化各个阶段的血清TBA浓度均会明显升高,但以晚期肝硬化最为明显^[6]。肝硬化患者还可能合并肝内胆-血屏障的损害,进一步加重血清TBA的升高^[7]。因此,在肝硬化失代偿期,即使肝细胞损伤较小,血清TBA也可以显著升高,且这些变化通常早于转氨酶等指标的变化^[8]。当肝硬化活动度降至最低,其他肝功能指标恢复正常时,血清TBA往往仍会处于升高状态。血清TBA水平对评估患者肝功能状态及预后具有重要的临床意义,并且可以作为Child-Pugh评分的有效补充。

2.1.3 HBA与胆汁淤积症 胆汁淤积症根据其胆汁流动中断发生的部位可分为肝内和肝外胆汁淤积^[9]。患肝内外胆汁淤积症时,血清TBA浓度均会显著升高^[9-10]。因而,血清TBA在鉴别肝内外胆汁淤积中的作用不大,但其在胆汁淤积症和高胆红素血症的鉴别方面有一定作用。胆汁淤积症时,TBA水平升高,胆红素通常保持正常;溶血等原因导致的高胆红素血症时,TBA水平通常是正常的;胆汁淤积性黄疸是胆汁淤积症的一个常见并发症,发生胆汁淤积性黄疸时,两者均升高^[11]。

原发性胆汁性胆管炎(primary biliary cholangitis, PBC)和原发性硬化性胆管炎(primary sclerosing cholangitis, PSC)同属于肝内胆汁淤积,两者胆汁酸谱存在重要差异:与PBC相比,PSC患者血清中的LCA和DCA水平较低^[12]。LCA和DCA是胆汁酸肠肝循环的指标,表明PSC的胆汁酸肠肝循环受到影响^[13]。DCA、CDCA和LCA对细胞活力和线粒体功能的影响比其他胆汁酸更大,因此,需要对患者胆汁酸谱进行全面分析,以充分掌握与胆汁酸升高相关的毒理学后果^[14-16]。一项研究发现,恶性胆道梗阻患者的TBA水平较良性梗阻有所升高,故TBA水平也可作为协助诊断良、恶梗阻性黄疸的一个参考指标,但该研究良、恶性梗阻组中血清TBA水平范围较大,存在一定的交叉,所以尚不能确定明显的区分界线^[17]。

2.1.4 HBA与脂肪肝 非酒精性脂肪性肝病(non-alcoholic steatohepatitis, NASH)的血清CA与CDCA的增加可能会促进胰岛素抵抗,DCA增幅比其他胆汁酸更加明显^[18-19]。胆汁酸谱变化的原因可能是饮食中的脂肪酸

改变了胆汁酸池中的胆汁酸成分,进而使肠道菌群发生改变^[20]。而肠道菌群在NASH的发生中起重要作用^[21]。虽然代谢相关脂肪性肝病(metabolic dysfunction-associated fatty liver disease, MAFLD)可以通过无创成像技术进行初步诊断,但目前仍需肝活检来评估,因此,亟需找到有效的循环生物标志物,以更好地识别需要进行活检的患者。胆汁酸可能有望成为鉴别单纯性脂肪肝和NASH的潜在候选指标。研究发现,NASH与单纯性脂肪肝患者相比,共轭初级胆汁酸显著升高^[19]。

2.1.5 HBA与肝胆疾病的预后 血清TBA水平下降缓慢通常提示预后不良;若TBA浓度再次升高或升高持续时间延长,则可能表明病情恶化或转为慢性。此外,TBA还可以作为活动期肝硬化和胆汁淤积性黄疸的敏感指标,如果治疗有效,其浓度会显著下降^[5]。

总之,在肝胆疾病的诊断中,血清TBA不仅比传统肝功能指标更为敏感和特异,还有助于判断疾病的转归及预后。胆汁酸谱有助于胆汁淤积性疾病的鉴别诊断。

2.2 HBA与妊娠 近年来,许多不孕不育及接受辅助生殖技术的女性在常规检查中发现血清TBA水平升高。多囊卵巢综合征以排卵障碍、雄激素水平过高和多囊卵巢为特征,是育龄期女性最常见的生殖内分泌紊乱疾病之一,常伴有HBA^[22]。妊娠期TBA水平会随孕周的增加而升高,但通常保持在正常范围内^[23]。妊娠期无症状HBA是指在妊娠期间没有发生肝胆系统疾病或出现任何妊娠期肝内胆汁淤积症的临床症状,但血清TBA浓度升至正常值的2倍以上^[24]。临床上可通过是否具有瘙痒症状来区分妊娠期无症状HBA和妊娠期肝内胆汁淤积症。LCA和DCA被发现可激活G蛋白偶联受体产生瘙痒反应^[25]。这两种疾病血清TBA水平无明显差异,但胆汁酸谱构成有显著区别,其临床特征和围生结局各不相同。因此,明确的临床诊断、合理的治疗和适当的产科处理对患者围生结局至关重要^[24,26]。

2.3 HBA与有机溶剂中毒 长时间接触肝毒性物质会导致肝损伤。四氯化碳、四氯乙烷和二甲苯等一些工业有机溶剂,对肝细胞有严重的损伤反应^[27-29]。然而,大部分常规肝功能检测,如转氨酶和 γ -谷氨酰转肽酶,对早期诊断中毒性肝病并不敏感^[30]。因此,需要更好的筛查方法来早期发现职业性和非职业性肝病。一项研究发现,87.7%的接触油漆厂有机溶剂的工人胆汁酸升高,胆汁酸水平与接触有机溶剂的时间和碳氢化合物接触评分呈正相关。而其他肝功能检测指标的平均水平均正常^[31]。通过受试者操作特征曲线和似然比评估TBA

与联合肝酶的性能,发现TBA的曲线下面积显著较高,且最佳决策水平为 $8\text{ }\mu\text{mol/L}$,因此血清TBA可作为筛查有机溶剂暴露的有效指标^[31-33]。

2.4 血清TBA与骨骼肌肉疾病 研究表明,胆汁酸参与骨骼和肌肉代谢^[34-36]。胆汁酸通过调节骨转换过程中的骨形成与骨吸收平衡来支持骨骼健康。相反,低水平或过量的胆汁酸则会促进骨吸收^[37]。骨质疏松症患者的胆汁酸水平常常发生变化。一项针对绝经后骨质疏松和骨质减少妇女的研究发现,血清TBA水平显著低于健康个体,并且与腰椎和髌部骨密度呈正相关^[38]。在健康成年人中也观察到了类似的结果^[36]。此外,血清TBA浓度与循环骨吸收标志物呈负相关,表明胆汁酸在调节骨结构方面具有潜在的保护作用^[36]。骨质疏松症患者不仅血清TBA浓度较低,还表现出胆汁酸池组成的改变,其中CA浓度高于CDCA^[36]。

此外,胆汁酸受体在肌肉细胞分化和肌肉肥大中也发挥重要作用,有助于改善肌肉功能^[39-40]。胆汁酸还可以独立于胆汁酸受体影响骨骼肌^[41]。在MAFLD患者中,血浆TBA浓度与骨骼肌体积呈负相关。并且DCA在MAFLD患者中表现出最强烈的失调,故DCA被认为是MAFLD相关肌肉减少症的潜在生物标志物。

2.5 HBA与遗传性疾病 部分遗传代谢性疾病可能导致血清TBA浓度升高。其中,进行性家族性肝内胆汁淤积(progressive familial intrahepatic cholestasis, PFIC)导致CA和CDCA水平升高^[9]。临床上PFIC以肝内胆汁淤积为主要表现,该病通常于婴儿期起病,极易进展为肝硬化,乃至肝衰竭^[42-43]。钠-牛磺胆酸共转运多肽缺陷病也是一种胆汁酸代谢异常的遗传性疾病,肝脏对胆汁酸的摄取受损,导致胆汁酸在血液中蓄积,主要表现为HBA,以结合型胆汁酸升高为主^[44]。婴幼儿主要表现为胆汁淤积性黄疸,而成年患者多数无症状,少数患者仅检测出血清TBA水平轻微升高,极少数也可表现为正常的血清TBA水平^[45]。与PFIC相比,这类患者临床预后较好。Alagille综合征是一种常染色体显性遗传病,临床表现多样,病情轻重不一^[46]。最常见的临床表型是肝脏受累,89%的患者可出现不同程度的胆汁淤积,表现为总胆红素、直接胆红素、总胆汁酸、碱性磷酸酶及天冬氨酸转氨酶的升高^[47-48]。Dubin-Johnson综合征是一种常染色体隐性遗传病,临床表现为反复发作的黄疸和长期或间歇性结合胆红素升高,实验室检查有时与Alagille综合征类似,但Dubin-Johnson综合征的血清TBA水平基本正常,预后较好^[49-50]。

3 总结与展望

综上所述,HBA是临床常见病症。多种病理状态均可引起血清TBA浓度及胆汁酸池组成的改变。本文旨在为临床医师提供HBA病因诊断的系统性思路,强调病因治疗是改善HBA的关键所在。通过明确病因,可为患者制订个体化治疗方案,从而改善临床预后。值得注意的是,多数HBA患者预后良好,这一认知有助于缓解患者的焦虑情绪。

利益冲突声明: 本文不存在任何利益冲突。

作者贡献声明: 李茂萍负责设计论文框架,起草论文;罗开忠负责论文修改,指导撰写文章并最后定稿。

参考文献:

- [1] WANG PW, DONG YW. Definition, etiology and classification of cholestasis[J]. J Intern Med Concepts Pract, 2022, 17(1): 15-23. DOI: 10.16138/j.1673-6087.2022.01.004.
汪佩文,董育玮.胆汁淤积的定义、病因及分类[J].内科理论与实践, 2022, 17(1): 15-23. DOI: 10.16138/j.1673-6087.2022.01.004.
- [2] ZHANG Y, LI JX, WANG YL. The role of bile acid metabolism and its receptors in the pathogenesis and progression of non-alcoholic fatty liver disease[J]. J Clin Hepatol, 2020, 36(6): 1374-1377. DOI: 10.3969/j.issn.1001-5256.2020.06.040.
张阳,李军祥,王允亮.胆汁酸代谢及其受体在非酒精性脂肪肝病发生发展中的作用[J].临床肝胆病杂志, 2020, 36(6): 1374-1377. DOI: 10.3969/j.issn.1001-5256.2020.06.040.
- [3] WINSTON JA, THERIOT CM. Diversification of host bile acids by members of the gut microbiota[J]. Gut Microbes, 2020, 11(2): 158-171. DOI: 10.1080/19490976.2019.1674124.
- [4] HAN CP, XU QF. Clinical application of serum total bile acid measurement in liver injury[J]. Med Innov China, 2013, 10(22): 84-85. DOI: 10.3969/j.issn.1674-4985.2013.22.040.
韩晨鹏,徐清芳.血清总胆汁酸测定在肝损伤中的临床应用[J].中国医学创新, 2013, 10(22): 84-85. DOI: 10.3969/j.issn.1674-4985.2013.22.040.
- [5] ZHANG JF, FU GS, WANG LH. Changes in serum bile acid levels in hepatitis patients and their clinical significance[J]. Chin J Clin Res, 1998, 11(5): 371-372.
张晶芬,付广双,王立红.肝炎患者血清胆汁酸含量变化及临床意义[J].中国厂矿医学, 1998, 11(5): 371-372.
- [6] LYU JL. Association between changes in serum total bile acids, albumin, and cholinesterase levels and Child-Pugh classification in patients with hepatitis and cirrhosis[J]. Pract Clin J Integr Tradit Chin West Med, 2021, 21(15): 113-114. DOI: 10.13638/j.issn.1671-4040.2021.15.056.
吕金龙.血清总胆汁酸、白蛋白、胆碱酯酶水平变化与肝炎肝硬化患者Child-Pugh分级的关联性[J].实用中西医结合临床, 2021, 21(15): 113-114. DOI: 10.13638/j.issn.1671-4040.2021.15.056.
- [7] LIU N, ZHOU YQ. The significance of bile acids in the progression and treatment of liver cirrhosis[J]. Chin Hepatol, 2022, 27(3): 376-379. DOI: 10.14000/j.cnki.issn.1008-1704.2022.03.021.
刘宁,周莹群.胆汁酸对肝硬化疾病进展及治疗的意义[J].肝脏, 2022, 27(3): 376-379. DOI: 10.14000/j.cnki.issn.1008-1704.2022.03.021.
- [8] NI YH, QIN DY, WANG L. Changes in serum levels of total bile acid, Golgi protein 73, and cancer antigen 19-9 in patients with cirrhosis and their clinical significance[J]. China J Gen Surg, 2024, 33(2): 305-310. DOI: 10.7659/j.issn.1005-6947.2024.02.019.

- 倪雅惠, 秦东媛, 王琳. 肝硬化患者血清总胆汁酸、高尔基体蛋白73及糖类抗原19-9的水平变化及其临床意义[J]. 中国普通外科杂志, 2024, 33(2): 305-310. DOI: 10.7659/j.issn.1005-6947.2024.02.019.
- [9] ZHU SS, LU X. Characteristics and research progress of serum bile acid profile in intrahepatic cholestasis[J]. Chin Hepatol, 2022, 27(6): 715-719. DOI: 10.14000/j.cnki.issn.1008-1704.2022.06.005.
- 朱时帅, 芦曦. 肝内胆汁淤积症血清胆汁酸谱的特征及研究进展[J]. 肝脏, 2022, 27(6): 715-719. DOI: 10.14000/j.cnki.issn.1008-1704.2022.06.005.
- [10] WU J, FAN Y, SHI G. Extrahepatic cholestatic jaundice[J]. J New Med, 2015, 25(1): 5-9.
- 吴杰, 范彦, 石干. 肝外胆汁淤积性黄疸[J]. 医学新知杂志, 2015, 25(1): 5-9.
- [11] LI X, ZHANG XL. Application of serum total bile acids in the diagnosis of hepatobiliary diseases[J]. Mod Med Health, 2006, 22(15): 2372. DOI: 10.3969/j.issn.1009-5519.2006.15.105.
- 李雪, 张筱丽. 血清总胆汁酸在肝胆疾病诊断中的应用[J]. 现代医药卫生, 2006, 22(15): 2372. DOI: 10.3969/j.issn.1009-5519.2006.15.105.
- [12] TROTTIER J, BIAŁEK A, CARON P, et al. Metabolomic profiling of 17 bile acids in serum from patients with primary biliary cirrhosis and primary sclerosing cholangitis: A pilot study[J]. Dig Liver Dis, 2012, 44(4): 303-310. DOI: 10.1016/j.dld.2011.10.025.
- [13] MONTE MJ, MARIN JJG, ANTELO A, et al. Bile acids: Chemistry, physiology, and pathophysiology[J]. World J Gastroenterol, 2009, 15(7): 804-816. DOI: 10.3748/wjg.15.804.
- [14] KRÄHENBÜHL S, FISCHER S, TALOS C, et al. Ursodeoxycholate protects oxidative mitochondrial metabolism from bile acid toxicity: Dose-response study in isolated rat liver mitochondria[J]. Hepatology, 1994, 20(6): 1595-1601. DOI: 10.1002/hep.1840200632.
- [15] PEREZ MJ, BRIZ O. Bile-acid-induced cell injury and protection[J]. World J Gastroenterol, 2009, 15(14): 1677-1689. DOI: 10.3748/wjg.15.1677.
- [16] SHARMA R, MAJER F, PETA VK, et al. Bile acid toxicity structure-activity relationships: Correlations between cell viability and lipophilicity in a panel of new and known bile acids using an oesophageal cell line (HET-1A)[J]. Bioorg Med Chem, 2010, 18(18): 6886-6895. DOI: 10.1016/j.bmc.2010.07.030.
- [17] HUANG HH, CHEN YY. Role of total bile acid determination in differential diagnosis of obstructive jaundice[J]. Med J Natl Defending Forces N China, 2006, 18(2): 105-107. DOI: 10.3969/j.issn.2095-140X.2006.02.012.
- 黄汇慧, 陈延演. 血清总胆汁酸测定在梗阻性黄疸鉴别诊断中的临床应用[J]. 华北国防医药, 2006, 18(2): 105-107. DOI: 10.3969/j.issn.2095-140X.2006.02.012.
- [18] JIAO N, BAKER SS, CHAPA-RODRIGUEZ A, et al. Suppressed hepatic bile acid signalling despite elevated production of primary and secondary bile acids in NAFLD[J]. Gut, 2018, 67(10): 1881-1891. DOI: 10.1136/gutjnl-2017-314307.
- [19] PURI P, DAITA K, JOYCE A, et al. The presence and severity of non-alcoholic steatohepatitis is associated with specific changes in circulating bile acids[J]. Hepatology, 2018, 67(2): 534-548. DOI: 10.1002/hep.29359.
- [20] DEVKOTA S, WANG YW, MUSCH MW, et al. Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in IL-10^{-/-} mice[J]. Nature, 2012, 487: 104-108. DOI: 10.1038/nature11225.
- [21] COPE K, RISBY T, DIEHL AM. Increased gastrointestinal ethanol production in obese mice: Implications for fatty liver disease pathogenesis[J]. Gastroenterology, 2000, 119(5): 1340-1347. DOI: 10.1053/gast.2000.19267.
- [22] DAPAS M, DUNAIF A. Deconstructing a syndrome: Genomic insights into PCOS causal mechanisms and classification[J]. Endocr Rev, 2022, 43(6): 927-965. DOI: 10.1210/endo/bnac001.
- [23] MCILVRIDE S, DIXON PH, WILLIAMSON C. Bile acids and gestation[J]. Mol Aspects Med, 2017, 56: 90-100. DOI: 10.1016/j.mam.2017.05.003.
- [24] LUO T, GUO XD, BAI XX. Research progress of asymptomatic hypercholanemia of pregnancy[J]. J Int Obstet Gynecol, 2021, 48(5): 499-502, 534. DOI: 10.12280/gjfcx.20210365.
- 罗挺, 郭雪冬, 白晓霞. 妊娠期无症状高胆汁酸血症的研究进展[J]. 国际妇产科学杂志, 2021, 48(5): 499-502, 534. DOI: 10.12280/gjfcx.20210365.
- [25] ALEMI F, KWON E, POOLE DP, et al. The TGR5 receptor mediates bile acid-induced itch and analgesia[J]. J Clin Invest, 2013, 123(4): 1513-1530. DOI: 10.1172/JCI64551.
- [26] CHEN X, SHAO Y, XU B, et al. A clinical analysis of asymptomatic hypercholanemia of pregnancy[J]. J Chongqing Med Univ, 2019, 44(8): 1059-1063. DOI: 10.13406/j.cnki.cyx.002147.
- 陈霄, 邵勇, 胥颢, 等. 妊娠期无症状高胆汁酸血症的临床特点分析[J]. 重庆医科大学学报, 2019, 44(8): 1059-1063. DOI: 10.13406/j.cnki.cyx.002147.
- [27] WANG RY. Combined serum bile acid concentrations in workers exposed to low doses of toluene and xylene[J]. J Prev Med Inf, 1991, 7(2): 118-119, 107.
- 王仁仪. 接触低剂量甲苯和二甲苯工人的结合血清胆汁酸浓度[J]. 预防医学情报杂志, 1991, 7(2): 118-119, 107.
- [28] LI NN, MENG XS, GUO WZ, et al. Effect of Ruangan chongji on CCl₄-induced hepatic fibrosis and intestinal flora in rats[J]. Liaoning J Tradit Chin Med, 2023, 50(4): 191-193, 228-229. DOI: 10.13192/j.issn.1000-1719.2023.04.050.
- 李楠楠, 孟宪生, 郭文昭, 等. 软肝冲剂对四氯化碳诱导大鼠肝纤维化及肠道菌群的影响[J]. 辽宁中医杂志, 2023, 50(4): 191-193, 228-229. DOI: 10.13192/j.issn.1000-1719.2023.04.050.
- [29] HUANG QZ, WANG CY. Clinical treatment and nursing of patients with liver damage caused by carbon tetrachloride poisoning[J]. Today Nurse (Specialist Edition), 2009, 16(10): 48.
- 黄清珠, 王翠玉. 四氯乙烯中毒致肝损害患者的临床救治与护理[J]. 当代护士(专科版), 2009, 16(10): 48.
- [30] LYU L, ZHANG GQ, JIN Y, et al. Clinical significance and research progress of changes in bile acid concentration in vivo[J]. J Clin Med Pract, 2013, 17(9): 159-161, 165. DOI: 10.7619/jcmp.201309063.
- 吕磊, 张国庆, 金彦, 等. 体内胆汁酸质量浓度变化的临床意义及研究进展[J]. 实用临床医药杂志, 2013, 17(9): 159-161, 165. DOI: 10.7619/jcmp.201309063.
- [31] EL HADY HM, METWALLY F, EL GENDY MF, et al. Serum bile acid as a screening tool in workers occupationally exposed to mixtures of organic solvents[J]. Toxicol Ind Health, 2014, 30(7): 645-652. DOI: 10.1177/0748233712462469.
- [32] NEGHBAB M, QU SX, BAI CL, et al. Raised concentration of serum bile acids following occupational exposure to halogenated solvents, 1, 1, 2-trichloro-1, 2, 2-trifluoroethane and trichloroethylene[J]. Int Arch Occup Environ Health, 1997, 70(3): 187-194. DOI: 10.1007/s004200050205.
- [33] CHEN JD, WANG JD, TSAI SY, et al. Effects of occupational and nonoccupational factors on liver function tests in workers exposed to solvent mixtures[J]. Arch Environ Health, 1997, 52(4): 270-274. DOI: 10.1080/00039899709602197.
- [34] YANG S, LI HY, GU YY, et al. The association between total bile acid and bone mineral density among patients with type 2 diabetes[J]. Front Endocrinol (Lausanne), 2023, 14: 1153205. DOI: 10.3389/fendo.2023.1153205.
- [35] ZHAO X, LIU ZT, SUN FY, et al. Bile acid detection techniques and bile acid-related diseases[J]. Front Physiol, 2022, 13: 826740. DOI: 10.3389/fphys.2022.826740.
- [36] LIU JX, CHEN YX, LUO Q. The association of serum total bile acids with bone mineral density in Chinese adults aged 20-59: A retrospective cross-sectional study[J]. Front Endocrinol (Lausanne), 2022, 13: 817437. DOI: 10.3389/fendo.2022.817437.
- [37] HERRMANN M, RODRIGUEZ-BLANCO G, BALASSO M, et al. The

- role of bile acid metabolism in bone and muscle: From analytics to mechanisms[J]. Crit Rev Clin Lab Sci, 2024, 61(6): 510-528. DOI: 10.1080/10408363.2024.2323132.
- [38] ZHAO YX, SONG YW, ZHANG L, et al. Association between bile acid metabolism and bone mineral density in postmenopausal women[J]. Clinics (Sao Paulo), 2020, 75: e1486. DOI: 10.6061/clinics/2020/e1486.
- [39] SASAKI T, KUBOYAMA A, MITA M, et al. The exercise-inducible bile acid receptor Tgr5 improves skeletal muscle function in mice[J]. J Biol Chem, 2018, 293(26): 10322-10332. DOI: 10.1074/jbc.RA118.002733.
- [40] YOSHIDA T, DELAFONTAINE P. Mechanisms of IGF-1-mediated regulation of skeletal muscle hypertrophy and atrophy[J]. Cells, 2020, 9(9): 1970. DOI: 10.3390/cells9091970.
- [41] OROZCO-AGUILAR J, TACCHI F, AGUIRRE F, et al. Ursodeoxycholic acid induces sarcopenia associated with decreased protein synthesis and autophagic flux[J]. Biol Res, 2023, 56(1): 28. DOI: 10.1186/s40659-023-00431-8.
- [42] ARONSON SJ, BAKKER RS, SHI XX, et al. Liver-directed gene therapy results in long-term correction of progressive familial intrahepatic cholestasis type 3 in mice[J]. J Hepatol, 2019, 71(1): 153-162. DOI: 10.1016/j.jhep.2019.03.021.
- [43] GUO J, XIE SY, YANG LR, et al. Clinical characteristics of 2 cases of progressive familial intrahepatic cholestasis and literature review[J/CD]. Chin J Liver Dis Electron Version, 2024, 16(1): 67-72. DOI: 10.3969/j.issn.1674-7380.2024.01.012.
郭静, 谢双宇, 杨玲蓉, 等. 进行性家族性肝内胆汁淤积症2例临床特点分析及文献复习[J/CD]. 中国肝脏病杂志(电子版), 2024, 16(1): 67-72. DOI: 10.3969/j.issn.1674-7380.2024.01.012.
- [44] LI H, CHEN R, LIN GZ, et al. Molecular epidemiology of Na⁺-taurocholate cotransporting polypeptide deficiency in Guangdong Province, China: A pilot study by screening for four prevalent variants of the causative gene SLC10A1[J]. Front Genet, 2022, 13: 874379. DOI: 10.3389/fgene.2022.874379.
- [45] ZHAO H, YU XM, BAI XX. Research progress on sodium-taurocholate cotransporting polypeptide deficiency disease and its impact on mother and fetus[J]. J Int Obstet Gynecol, 2023, 50(6): 684-688. DOI: 10.12280/gjfcx.20230675.
赵欢, 余晓明, 白晓霞. 钠离子牛磺胆酸共转运多肽缺陷病及其对母胎影响的研究进展[J]. 国际妇产科学杂志, 2023, 50(6): 684-688. DOI: 10.12280/gjfcx.20230675.
- [46] IBRAHIM SH, KAMATH BM, LOOMES KM, et al. Cholestatic liver diseases of genetic etiology: Advances and controversies[J]. Hepatology, 2022, 75(6): 1627-1646. DOI: 10.1002/hep.32437.
- [47] KOHUT TJ, GILBERT MA, LOOMES KM. Alagille syndrome: A focused review on clinical features, genetics, and treatment[J]. Semin Liver Dis, 2021, 41(4): 525-537. DOI: 10.1055/s-0041-1730951.
- [48] WU LN, SUN LY, ZHU ZJ, et al. Clinical and histological characteristics of patients with Alagille syndrome[J]. Chin Hepatol, 2023, 28(3): 351-354, 363. DOI: 10.14000/j.cnki.issn.1008-1704.2023.03.018.
武丽娜, 孙丽莹, 朱志军, 等. Alagille 综合征的临床及病理特征分析[J]. 肝脏, 2023, 28(3): 351-354, 363. DOI: 10.14000/j.cnki.issn.1008-1704.2023.03.018.
- [49] SIDDIQUI AH, ALSABE MR, TEHSEEN Z, et al. Dubin-Johnson syndrome: A case report[J]. Cureus, 2023, 15(3): e36115. DOI: 10.7759/cureus.36115.
- [50] WANG YL, QIAO HJ, DONG YH, et al. Clinical characteristics analysis of 11 cases of Dubin-Johnson syndrome[J]. Henan Med Res, 2022, 31(24): 4437-4441. DOI: 10.3969/j.issn.1004-437X.2022.24.004.
王亚丽, 乔会菊, 董燕红, 等. 11例Dubin-Johnson综合征患者临床特征分析[J]. 河南医学研究, 2022, 31(24): 4437-4441. DOI: 10.3969/j.issn.1004-437X.2022.24.004.

收稿日期: 2024-08-07;录用日期: 2024-09-30

本文编辑: 林蛟

引证本文: LI MP, LUO KZ. Common etiology and diagnosis of hyperbileacidemia[J]. J Clin Hepatol, 2025, 41(5): 991-995.

李茂萍, 罗开忠. 高胆汁酸血症的常见病因及诊断[J]. 临床肝胆病杂志, 2025, 41(5): 991-995.

· 致谢 ·

本期审稿专家 Current reviewers

王 甦	王睿林	王震侠	毛靖伟	孔 丽	孔 明	孔 静	卢军华	叶卫江	史宪杰	庄立琨
刘先治	刘志华	刘银坤	刘燕敏	许翠萍	孙文兵	纪泛扑	苏海滨	李 伟	李志勤	李 威
李婉玉	李 筠	李 磊	杨 丽	杨晋辉	杨盛力	连建奇	汪习成	张小勇	张 伟	张 威
陈世耀	陈 钟	陈 洪	陈 晶	罗剑钧	岳树强	金 洁	郑文杰	赵卫峰	赵丹彤	赵文静
赵 平	赵东强	赵守松	郝建宇	施维群	袁 静	夏光涛	夏时海	徐铭益	郭进军	唐映梅
彭海燕	舒慧君	雷光林	福军亮	管青天	樊和斌	薛 挥				