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述评 EDITORIAL

胆管消失综合征的再认识

陈 芳, 涂相林

陈芳, 南昌大学附属感染病医院, 南昌市第九医院肝三科 江西省南昌市 330002

涂相林, 南昌大学附属感染病医院, 南昌市第九医院感染一科 江西省南昌市 330002

涂相林, 主任医师, 硕士研究生导师, 主要从事病毒性肝炎慢性化、肝硬化、药物性肝损害的基础与临床研究.

作者贡献分布: 本文由陈芳与涂相林共同完成.

通讯作者: 涂相林, 主任医师, 硕士生导师, 330002, 江西省南昌市洪都中大道167号, 南昌市第九医院感染一科.
tuxl_01@163.com
电话: 0791-88499600

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Revaluation of vanishing bile duct syndrome

Fang Chen, Xiang-Lin Tu

Fang Chen, Third Department of Liver Diseases, the Affiliated Infectious Hospital of Nanchang University and the Ninth Hospital of Nanchang, Nanchang 330002, Jiangxi Province, China

Xiang-Lin Tu, First Department of Infectious Diseases, the Affiliated Infectious Hospital of Nanchang University and the Ninth Hospital of Nanchang, Nanchang 330002, Jiangxi Province, China

Correspondence to: Xiang-Lin Tu, Chief Physician, First Department of Infectious Diseases, the Affiliated Infectious Hospital of Nanchang University and the Ninth Hospital of Nanchang, 167 Hongdu Middle Avenue, Nanchang 330002, Jiangxi Province, China. tuxl_01@163.com

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Abstract

Vanishing bile duct syndrome (VBDS) can result from multiple etiologies, including congenital and genetic diseases, ischemic causes, neoplastic disorders, infections, immune disorders, drugs, idiopathic adulthood ductopenia (IAD) and so on. Recently, lymphoma, HIV/AIDS and drugs were identified to be major etiologies in the reported cases, some of which presented complex clinical course and were contributed by more than one etiological factor. Hepatic biopsy must be done for the diagnosis of VBDS and immunohistochemical staining for cytokeratin 7 (CK7) and CK19 has contributed to the establishment of diagnosis of VBDS. VBDS can be usually treated with symptomatic and supportive therapy, etiological therapy, liver transplantation, ursodeoxycholic acid and immunosuppressive agents. Glucocorticoids can be tried to switch to mycophemolate mofeil or tacrolimus when their effects are poor or side effects are severe. Severe cases ought to receive multimodality therapy besides plasmapheresis.

Key Words: Vanishing bile duct syndrome; Etiology; Diagnosis; Therapy

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摘要

胆管消失综合征(vanishing bile duct syndrome,

背景资料
胆管消失综合征(vanishing bile duct syndrome, VBDS)最早见于婴幼儿肝内胆道闭锁以及相关的儿科肝脏疾病, 以后不断发现许多病因可以引起VBDS, 自从Sherlock系统提出VBDS概念以来, VBDS的病因不断得到补充完善, 对病因的了解有助于对VBDS的早期诊断和治疗有重要意义.

同行评议者
王刚, 副研究员, 哈尔滨医科大学附属第一医院胰胆外科(普外二科)

研发前沿
VBDS病因较多且复杂, 有的病例可能有两个以上的因素参与, 尤其是重症病例. 治疗目前仍然是难点, 熊去氧胆酸(ursodeoxycholic acid, UDCA)无应答时免疫抑制剂的选择, 重症病例的综合治疗措施都有待于临床研究和经验总结.

VBDS)病因较多, 主要有先天性和遗传性疾病、缺血缺氧、肿瘤、感染、免疫紊乱、药物、特发性成人肝内胆管缺失症等因素. 近年报道比较多的病因是淋巴瘤、HIV感染/AIDS和药物, 有些VBDS病例较复杂, 可能不止一种因素参与. VBDS的诊断需要肝脏组织学检查, 肝组织角蛋白7(cytokeratin 7, CK7)和CK19免疫组织化学检查有助于提高VBDS诊断的可靠性. VBDS的治疗主要是对症支持治疗、病因治疗、肝移植、熊去氧胆酸和免疫抑制剂的应用, 糖皮质激素疗效不好或不良反应明显时可以试换用吗替麦考酚酯或他克莫司, 重症病例强调包括血浆置换的综合治疗.

关键词: 胆管消失综合征; 病因学; 诊断; 治疗

核心提示: 近年来不断有胆管消失综合征(vanishing bile duct syndrome, VBDS)病例报道, 病因主要是淋巴瘤、人类免疫缺陷病毒感染/艾滋病和药物, 肝组织角蛋白7(cytokeratin 7, CK7)和CK19免疫组织化学检测有助于提高VBDS诊断的可靠性. 熊去氧胆酸仍然是治疗VBDS相对有效的药物.

陈芳, 涂相林. 胆管消失综合征的再认识. 世界华人消化杂志 2016; 24(23): 3445-3453 URL: http://www.wjgnet.com/1009-3079/full/v24/i23/3445.htm DOI: http://dx.doi.org/10.11569/wcjd.v24.i23.3445

0 引言

肝内胆管缺乏和肝内胆管发育不良最早见于婴幼儿肝内胆道闭锁以及相关的儿科肝脏疾病的描述[1,2], 后来发现许多原因可以导致肝内胆管缺乏或消失, Sherlock[3]真正系统提出胆管消失综合征(vanishing bile duct syndrome, VBDS)概念, 其对VBDS的病因学进行了归纳分类. 由于VBDS病因较多, 临床表现缺乏特异性, 在我国肝穿刺组织活检术没有广泛开展, 因此, 有必要加强对VBDS的认识. 自从VBDS的概念被提出以来, 临床上不断有VBDS病例的报道. 本文就VBDS的相关进展进行综述, 旨在进一步提高对VBDS的认识, 为临床诊疗提供帮助.

1 病因学

由于VBDS缺乏临床特异性, 因此, 找出病因是诊断和治疗的关键. 下面就VBDS的可能病因进行叙述.

1.1 先天性和遗传性疾病 先天性和遗传性疾病出现胆管缺失原因复杂, Reau等[4]的分类方法有参考价值. 胆管发育过程障碍往往表现为新生儿胆汁淤积(neonatal cholestasis, NC). 但NC的原因多种多样, 其中胆道闭锁是NC的重要原因[5], 但是, 要鉴别NC中的胆道闭锁患者是一件比较困难的事情, 尽管有研究[6]显示没有一个敏感性和特异性比较好的临床特征供临床使用, 但在最近, 有应用以肝胆亚氨二醋酸(hepatobiliary iminodiacetic acid, HIDA)扫描为基础的诊断推导方法在排除胆道闭锁有帮助[7]. 在遗传性疾病中, Alagille Syndrome属于遗传性疾病中的综合征类型, 诊断仍然是临床的难点. 最近有研究[8]提示, 角蛋白7(cytokeratin 7, CK7)和上皮膜抗原(epithelial membrane antigen, EMA)有助于鉴别Alagille Syndrome的胆管缺失.

1.2 缺血缺氧 肝移植后出现VBDS的病例大多数见于早期报道. 尽管肝移植后VBDS的原因有很多, 但肝移植手术本身引起的肝动脉血流减少、移植物抗宿主排异反应导致的肝脏内动脉闭塞、肝动脉炎等导致胆管损伤乃至VBDS[9]. 肝移植后的门静脉腔变小、门静脉血流减少也与缺血性胆管损伤有关[10,11]. 胆道缺血缺氧还与供肝的冷缺血时间和/或热缺血时间过长、慢性排斥反应等有关. 一项单中心研究[12]也发现, 无论是冷缺血时间还是热缺血时间, 都是肝移植后胆管损伤的独立危险因素. 胆道系统的缺血缺氧可引起胆道上皮细胞缺血性坏死和胆管生成障碍, 最终导致VBDS.

1.3 肿瘤因素 自从Hubscher等[13]报道何杰金氏淋巴瘤(Hodgkin's lymphoma, HL)伴有肝内胆汁淤积和VBDS现象以来, 以后陆续有较多的相关病例被报道[14]. VBDS一般在HL被诊断以后出现, 有的甚至是在尸检时发现, 肝内胆汁淤积和VBDS有时被当作HL的临床表现之一. 但是有的HL最先出现的却是VBDS的临床表现, 过后才诊断HL[15,16], 这容易对临床治疗造成影响. 有临床病例报道显示[17-20]: 伴有VBDS的HL患者, 在HL经过成功治疗以后, VBDS也得到改善和逆转, 因此, 对于HL相关的VBDS, 及时治疗原发病是关键.

较早就有报道非何杰金氏淋巴瘤(non Hodgkin's lymphoma, NHL)存在VBDS现象,

患者均存在多种基础疾病, 治疗效果都不理想[21,22]. 后来报道的1例NHL病例, 经过几个疗程化疗, 病情得到缓解[23], VBDS也得到了改善. 上述3例患者有2例存在EB病毒(epstein-barr virus, EBV)感染的依据, EBV是否参与了VBDS的发生尚不能确定. 新近也有报道间变性大细胞淋巴瘤[24]和弥漫性大B细胞淋巴瘤[25]合并VBDS的报道, 2例患者经过抗肿瘤化疗后, 病情都得到了明显改善. 从通过化疗缓解病例推测: NHL引起VBDS, 类似HL引起VBDS, 既有浸润癌细胞的作用, 也有肿瘤细胞释放的细胞因子产生癌旁效应所致[13], 根本仍是治疗原发病. 另外, 仅有朗罕氏组织细胞增生症和巨噬细胞活化综合征导致的VBDS的单个病例报道[26,27], 以后有待积累和总结.

1.4 感染因素 有许多感染性因素与VBDS有关, 尤其是新生儿期. 新生儿早期暴露于巨细胞病毒(cytomegalovirus, CMV)、3型呼肠孤病毒(reovirus 3)、梅毒、风疹病毒与VBDS有关[3,4].

CMV感染是我国儿童胆道闭锁的重要病原[28,29], 也是儿童VBDS的常见病因[30]. CMV引起VBDS较早报道最多的是肝移植患者, 但CMV引起VBDS的观点并不一致, 似乎CMV不起主要作用[31-35]. 乙型肝炎病毒(hepatitis B virus, HBV)和HCV均可引起VBDS, 但以HCV多见[36-38].

HCV感染不仅在肝移植中导致VBDS, 在肾移植中的受体肝脏也出现VBDS[39-41], 可见HCV引起VBDS不仅多见, 而且复杂. 对于实体器官移植患者, 不仅要监测CMV感染, 监测HCV感染同样重要, 尤其是出现肝炎表现或胆汁淤积的情况下. 戊型肝炎临床表现多有黄疸和肝内胆汁淤积, 无论是戊型肝炎病毒感染还是重叠HBV感染, 我国有限的肝脏组织病理学上研究均未见小叶间胆管的破坏或消失[42-44], 仅有个案报道[45]戊型肝炎患者表现为炎症性胆管损伤.

在免疫抑制状态下容易出现EBV感染, 但EBV导致VBDS的报道比较少见, 已有的EBV引起VBDS报道病例[46]显示: 患者在使用大剂量免疫抑制剂后出现EBV感染, 随后出现VBDS. 这种情况与CMV有点相似.

人类免疫缺陷病毒(human immunodeficiency virus, HIV)感染进展至艾滋病(acquired immune deficiency syndrome, AIDS)阶段, 往往存在明显的免疫功能低下. 较早报道[47]的进展期AIDS患者存在VBDS同时有HCV和CMV感染的依据, 但没有接受过高效抗逆转录病毒治疗(highly active antiretroviral therapy, HAART), 后续报道的AIDS患者治疗经过复杂, 有的存在使用多种抗生素和布洛芬的历史, 几乎都在接受HAART后出现VBDS[48-52], 这种情况可能免疫反应参与了这一过程. 由于AIDS患者的机会性感染、复杂的治疗经过和本身的HAART, 有的可能已经有药物性因素等多种因素参与了VBDS的过程, 所以现在将AIDS患者胆管受损统称为AIDS相关胆管病变, AIDS患者感染的隐孢子虫属、CMV、微孢子虫属是引起AIDS相关胆管病变的主要病原体[53,54].

1.5 免疫因素 VBDS被认为是免疫介导的胆管相关性疾病[55], 免疫损伤胆管系统是引起VBDS的重要机制. 原发性胆汁性胆管炎(primary biliary cholangitis, PBC)、免疫性胆管炎、原发性硬化性胆管炎(primary sclerosing cholangitis, PSC)结节病、移植免疫都与免疫有关, 可以引起VBDS[4]. 多形红斑是由免疫介导的皮肤和/或黏膜损害[56], 有儿童多型红斑后出现VBDS的报道[57], 但该患者在VBDS出现前有使用阿莫西林和乙酰氨基酚的历史, 故该患者的VBDS可能有多因素参与. 中毒性表皮坏死松解症(toxic epidermal necrolysis, TEN)是多形红斑的严重类型, VBDS合并TEN的病例也见报道[58,59], 被认为是对药物的超敏反应[58]. 国内的研究[60]显示: PBC患者约有62.6%存在小胆管减少或消失. 甲状腺功能减退也是与免疫相关的疾病, 也见甲状腺功能减退症合关VBDS的报道[61]. 大多数感染性因素导致的VBDS存在免疫介导损伤的证据, 严重的药物性肝损害(drug-induced liver injury, DILI)也与免疫有关[58]. 可见, 寻找免疫状态异常信息对明确VBDS有帮助.

1.6 药物 临床上引起VBDS最多见的病因是药物, 也是报道病例中最多的. 但是, 药物引起的VBDS又是最复杂的一种, 可能最先表现为DILI, 后来发展为VBDS, 且有些病例表现为不可逆. 因此, 了解哪些药物可以导致VBDS很重要, 孙玥等[62]对药物相关性VBDS进行过综述, 对临床有指导作用. 引起VBDS的药物比较多, 如抗生素类的阿莫西林或/和克拉维酸钾、阿奇霉素、莫西沙星、美罗培南、抗HIV的奈韦

相关报道
Sherlock于1987年在《Lancet》上提出VBDS概念是里程碑式的, 到2008年, Reau在《Clinicsin Liver Disease》上系统地完善了VBDS的概念、病理、病因、临床表现和治疗, 对临床VBDS的诊疗起到了指导作用. 2014年贾继东教授等在《肝脏》杂志上发表了VBDS病因学诊断及预后进展和药物相关VBDS诊断及治疗进展的综述, 对我国临床医生认识理解VBDS大有帮助.

创新盘点

本文重点总结了近年报道的VBDS病例, 对感染性因素作了全面的总结, 对其中一些报道的病例进行了病因学分析, 进一步总结了VBDS的病例特点, 提出了VBDS的诊断思考.

拉平等, 非甾体类抗炎药布洛芬、洛索洛芬等, 抗精神类药、抗肿瘤类药等, 并且报道药物相关VBDS的病例还会增多.

近年报道的抗生素类有环丙沙星、磺胺类的复方新诺明(SMZ-TMP)、左氧氟沙星. 环丙沙星可导致VBDS合并Stevens-Johnson综合征(Stevens-Johnson syndrome, SJS)[63], 病情较重, 这种合并症以前也见报道[64,65]. 临床上SMZ-TMP引起过敏反应比较常见, 但引起VBDS也偶见报道, 且成人和儿童均可出现[66,67]. 左氧氟沙星像其他喹诺酮类药物一样, 可以引起DILI, 但左氧引起的DILI更重[68,69]. 左氧引起VBDS仅见1例报道, 但这位患者合并有甲减[70], 不排除有甲减的因素参与了VBDS的过程.

非甾体类抗炎药中的对乙酰氨基酚被认为是发达国家肝损害中最常见的病因[71], 但其引起VBDS的病例近年也仅见1例报道[72], 且是VBDS合并SJS, 症状重, 最终进行肝移植治疗. 抗精神病药氯丙嗪、唑尼沙胺、丙戊酸、卡马西平、拉莫三嗪导致VBDS已为大家熟知[62], 许多抗精神病药、抗抑郁药与肝损害甚至肝衰竭有关[73], 近年有奥卡西平和舍曲林引起VBDS的病例报道. 奥卡西平是用于局限性及全身性癫痫发作的抗精神病药, Tekin等[74]报道的奥卡西平相关VBDS患者, 既往有干燥综合征病史, 且最后出现噬血细胞综合征, 不能排除免疫因素参与. 舍曲林是用于治疗抑郁症的相关症状的抗精神病药, Conrad等[75]报道的舍曲林相关VBDS患者, 在使用舍曲林5 mo后出现VBDS, 但在停药后肝功能逐渐恢复正常, 说明舍曲林相关VBDS愈后不严重且可逆.

替莫唑胺是一种抗肿瘤的烷化剂, 主要用于神经胶质母细胞瘤的治疗. 最近有2例替莫唑胺相关VBDS报道. Mason等[76]报道的患者在替莫唑胺化疗后出现VBDS, 但停药后肝功能恢复. Balakrishnan等[77]报道的患者在使用替莫唑胺后先表现为DILI的病理表现, 后进展为VBDS, 但这位患者同时服用了SMZ-TMP, 并不能完全排除SMZ-TMP的因素对VBDS的作用.

总之, 药物相关的VBDS非常复杂, 有些病例可能是多种因素参与, 但是这些病例报道出来可以引起大家的重视, 通过大家的关注, 不断积累经验, 做到早发现、早治疗, 改善患者预后.

1.7 特发性成人肝内胆管缺失症

特发性成人肝内胆管缺失症(idiopathic adulthood ductopenia, IAD)的发病率较低, Ludwig等[78]提出的IAD诊断标准, 目前仍然被大家所引用[62,79]. 由于引起慢性胆管炎或肝内胆管缺失的病因多样和复杂, IAD的病因具有明显的异质性和不确定性, 临床过程和愈后差别都很大, 因此IAD的诊断仍然是排他性的[80].

2 诊断

VBDS主要是胆汁淤积的临床表现, 但是有的VBDS没有胆汁淤积的表现, 因此, VBDS主要依靠肝脏组织学检查来确诊, 必须进行肝穿刺活检. 目前, 就VBDS的诊断还没有一个专家共识. 至于肝内胆管缺失多少就考虑VBDS, 在肝移植后并发的VBDS和IAD的诊断标准中, 都是选择汇管区小叶间胆管至少缺失50%, 为求准确, 肝组织活检标本中应至少包括11个以上的汇管区, 理想的状态是不少于20个汇管区[78,81]. 目前国内也是选择这个标准用于各种病因引起的VBDS[82-84]的诊断. 肝组织CK7、CK19免疫组织化学可以显示肝内小胆管的数量与分布[85], 有助于提高VBDS诊断的准确性, 也被用于一些VBDS病例的辅助诊断[86-88]. 由于VBDS的形成是一个小胆管炎症逐渐进展的结果, 因此, 在病程的哪个阶段取标本很关键, 尤其是药物诱导的VBDS, 早期可能是DILI的表现. 所以可疑VBDS的患者多次肝活检更合理, 结果才更可靠.

3 治疗

VBDS的病因较多, 治疗应是根据不同的病因和临床表现采用不同的治疗方法, 总体策略包括对症支持治疗、停用可能引起VBDS的药物、潜在感染的治疗、熊去氧胆酸(ursodeoxycholic acid, UDCA)和免疫抑制剂的应用[4,77]. 另外, 原发病的治疗也很重要, 如上述中有一部分淋巴瘤合并VBDS患者经化疗后, VBDS随淋巴瘤病情缓解而改善. 由于毛细胆管再生能力差, 许多VBDS患者最终行肝移植治疗. 肝移植本身也是VBDS的一个病因, 移植后抗排斥药对肝移植后VBDS也有治疗作用.

根据VBDS的病理特点, 大多数患者首选了UDCA和糖皮质激素治疗, 疗效不好或不良反应明显时可将糖皮质激素换用吗替麦考酚酯[89], 也有将糖皮质激素换用他克莫司(Tacrolimus)治愈的报道[63]. VBDS有合并症或

存在并发症时应给予综合治疗, 出现肝衰竭可以应用包括血浆置换的人工肝支持系统治疗, 以便等待肝移植, 也有经UDCA治疗无应答的VBDS患者最后行血浆置换治疗达到缓解[90]. 以上病例多为个案, 有待以后探索和总结.

4 诊治体会

南昌市第九医院近7年通过肝活检病理学诊断VBDS病例共21例, 其中临床拟诊DILI的42例, 病理诊断VBDS 2例, 临床拟诊PBC、黄疸待查、肝功能异常查因、不明原因肝硬化共32例, 病理诊断VBDS 19例, 其中3例第一次肝活检考虑DILI, 因治疗效果欠佳于半年后第二次肝活检诊断VBDS. 对于PBC和不明原因肝硬化的VBDS患者, UDCA或糖皮质激素大多疗效不佳. 对于药物相关的VBDS, UDCA 20 mg/(kg•d)[67]有一定的疗效, 有些患者在服药1-2年后, 维持5 mg/(kg•d)可以使患者生化指标在大致正常范围, 但有1例患者在维持上述剂量后3 mo生化指标反弹, 目前仍然20 mg/(kg•d)维持, 仍在随访中. 重症患者因为肝组织来源困难, 没有诊断和治疗经验. 药物相关VBDS发病过程相对长些, 一次肝活检可能不能满足诊断需要. UDCA仍然是治疗药物相关VBDS的有效药物, 但没有停药经验.

5 结论

随着VBDS逐渐被大家所认识, 诊断的病例会越来越大多. 由于VBDS的病因较多, 在相关病因的诊治过程中, VBDS作为一种合并症会被更多的人所关注, 有一些VBDS会更早地被发现, 大大地改善了患者的病情进展和预后. 基于VBDS发病机理, 已有实验研究为治疗VBDS探索新途径, 如应用αvβ6整合素抑制剂、索拉非尼(Sorafenib)等抑制小胆管纤维化[91], 胰高血糖素样肽1受体激动剂: Exendin-4阻止胆管细胞凋亡[92]. 最近, 有应用逆转录酶抑制剂治疗UDCA无应答的PBC患者和应用逆转录酶抑制剂和蛋白酶抑制剂治疗合并HIV感染的PBC患者的临床试验, 达到了生化指标的改善[93], 值得扩大样本进一步研究.

总之, 近年报道比较多的VBDS病因是淋巴瘤、HIV感染/AIDS和药物, 有些VBDS病例较复杂, 可能不止一种因素参与. 肝组织CK7和CK19免疫组织化学检查有助于提高VBDS诊断的可靠性. UDCA和免疫抑制剂的应用、病因治疗仍然是VBDS的主要治疗手段.

应用要点

本文所总结的VBDS病因、诊断治疗分析, 对临床中出现胆汁淤积、不明原因肝损害、不明原因黄疸、不明原因肝硬化等一些疑难病的诊断有指导作用, 并且可以使得VBDS的诊断更可靠, 对一些复杂和重症患者治疗有借鉴作用.

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名词解释

汇管区: 又称门管区, 是由相邻几个肝小叶角缘处的结缔组织构成, 内有小叶间静脉、小叶间动脉和小叶间胆管.

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同行评价

本文对胆管消失综合征这一临床罕见疾病的研究进展做了较为详细的归纳与总结, 为广大临床医师加深对此病的认识和理解提供了一个有效的平台, 具有较好的临床意义.

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