

蓝氏贾第鞭毛虫感染的免疫学诊断方法

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Immunological diagnosis of *Giardia lamblia* infection

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Abstract

Giardia lamblia infection causes diarrhea in human beings and other mammals, and it is attracting more and more attention in recent years. In this article, we reviewed immunological methods for the diagnosis of *Giardia lamblia* infection, compared the advantages and disadvantages of several diagnostic approaches, and briefly introduced some commercial kits, which would bring lots of conveniences to clinical diagnosis, therapy, and prognosis of Giardiasis.

Key Words: Immunological diagnosis; *Giardia lamblia*; Infection

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摘要

蓝氏贾第鞭毛虫感染可引起人及其他哺乳动

物腹泻。近年来, 贾第虫病的严重性和危害性日益受到重视。本文对蓝氏贾第鞭毛虫感染的免疫学诊断方法研究进行了综述, 比较了各种方法的优缺点, 简要介绍了一些商品化试剂盒的使用情况。贾第虫病免疫学诊断方法的应用, 对贾第虫病的临床诊断、治疗、预后将带来极大的方便。

关键词: 蓝氏贾第鞭毛虫; 免疫学诊断; 感染

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0 引言

蓝氏贾第鞭毛虫(*Giardia lamblia*), 简称贾第虫, 是一种引起人及其他哺乳动物腹泻的机会性致病寄生虫。无论在工业发达国家或发展中国家均有本虫的广泛流行^[1]。在美国将贾第虫称为“头号肠道寄生虫”, 该国的一项调查估计每年有 2.8×10^6 人感染蓝氏贾第鞭毛虫^[2]。在意大利研究表明感染蓝氏贾第鞭毛虫可加重肠易激综合征^[3]。法国则发现肠源性脂肪代谢障碍的发病与其有关^[4]。在发展中国家, 感染人数估计为2.5亿^[5]。本虫在我国的流行也相当广泛, 感染率各地区不等, 约在1%-10%左右^[6]。其滋养体引起的贾第虫病已被列为全世界危害人类健康的十种主要寄生虫病之一^[7]。最新研究证明, 蓝氏贾第鞭毛虫合并HIV/AIDS的感染, 及其在同性恋者中流行的报道不断增多^[8]。本病除地方性流行、暴发外, 在旅游者中感染也甚常见, 故有“旅游者腹泻(traveller's diarrhea)”之称^[9]。因此, 贾第虫病的严重性和危害性日益受到重视。本文就近年来贾第虫病的免疫学诊断方法的研究综述如下。

1 酶联免疫吸附测定法 (ELISA)

1.1 检测抗原 ELISA是免疫学试验中应用最普遍、适用范围最广的一种免疫酶标记检测技术^[10-11]。检测贾第虫抗原的敏感性为100%、特

■背景资料

蓝氏贾第鞭毛虫寄生于人和哺乳动物的小肠, 引起以腹泻为主要症状的贾第虫病(giardiasis), 贾第虫病呈世界性分布, 是最常见的胃肠道寄生虫。贾第虫病的诊断主要是通过粪便检查, 免疫学诊断方法为贾第虫病的流行病学调查、疗效考核、感染源的筛查提供了捷径。

■研发前沿

贾第虫病的诊断主要是通过粪便检查,但费时费力,而且对操作人员的技术水平要求较高,故免疫学诊断方法对于贾第虫病的易感人群,尤其是免疫力低下的患者(如儿童、老人、AIDS等)的诊断、治疗、预后及随访有很大帮助,目前国外已研发出许多商品化的试剂盒更方便、快速。

异性为91.67%(Ali *et al*, 2003)^[12]. 该检测法与患者粪便中包裹的计数、粪便的性状(血便、黏液便、脂肪泻)及年龄无显著的相关性,却与恶心、腹胀、腹痛、腹泻、食欲减退、体重减轻、乏力(除外呕吐及便秘)等消化道症状呈正相关,贾第虫包裹在稀质粪便中计数较高^[13-14].

Nakaya *et al*^[15]用哥伦比亚贾第虫病患者粪便中的包裹(包裹经蔗糖梯度离心法提纯)和感染贾第虫的长爪沙鼠体内的滋养体,接种家兔以获得不同阶段的抗贾第虫IgG抗体(经正辛酸和硫酸铵沉淀法纯化)用于检测患者粪便中的抗原. 该法捕获贾第虫抗原最适多克隆抗体浓度为40克/毫升,最适的稀释倍比浓度为1:100,消光值(OD)为0.24^[16-17]. 对196份患者粪便样本的寄生虫学检验,69份粪便样本中查到了贾第虫包裹,56份粪便样本中未见贾第虫包裹,71份粪便样本中可见其他寄生虫,其敏感性为100%(95% CI: 93.4-100%);特异性为95% (95% CI: 88.6-97.6%);阳性预测(价)值为91% (95% CI: 81.4-95.9%);阴性预测(价)值为100% (95% CI: 96.1-100%)^[15]. 故认为ELISA法可提高诊断贾第虫的阳性率,并且可用于贾第虫治疗后的随访^[18-20].

1.1.1 斑点-ELISA (DOT ELISA) 以硝酸纤维素(NC)多孔薄膜作为固相载体,预先将贾第虫抗体点涂于NC膜上,以吸附粪便样本中的抗原,阳性反应在NC膜上呈现有色斑点,阴性对照为无色. Rashid *et al*用DOT-ELISA法检测200名1-13岁的埃及患儿(主要是腹痛、腹泻、食欲减退、体重减轻和维生素缺乏等相关症状),其阳性率为24.5%、敏感性为100%、特异性为93.8%^[21]. 该法操作简单、反应快速、肉眼判断结果、直观且可保留结果以利复查,适于现场调查.

1.1.2 双抗体夹心法-ELISA (double antibody sandwich ELISA) 应用色谱仪纯化抗溶组织阿米巴、贾第虫、隐孢子虫的抗血清,检测埃及90名患者粪便样本中相应的抗原. 40名年龄相近的对照组中,20名是其他寄生虫的感染者(阳性对照组),另20名为无肠道寄生虫感染者(阴性对照组). 该法检测溶组织阿米巴和贾第虫感染的阳性率为100%,隐孢子虫感染的阳性率为96.6%,检测溶组织阿米巴、贾第虫、隐孢子虫粪抗原的假阳性例数分别为5(87.5%)、3(92.5%)、2(95%)^[22]. 粪抗原的平均值水平随感染的症状加重而增加,而与年龄无明显相关性^[23].

1.1.3 抗原捕获法-ELISA (antigen-capture ELISA) 贾第虫的病原学诊断是在显微镜下查

到贾第虫的包裹或滋养体,此法费时费力,而且对操作人员的技术要求也较高,容易漏检^[24]. Jelinek *et al*^[25]分别用显微镜(铁苏木素染色和SAF浮聚法)和ELISA试剂盒检测795名德国慕尼黑患者的粪便样本,以便了解海外旅游者中贾第虫病的患病率,其中74位患者确诊为贾第虫感染. ELISA试剂盒(95.5%)较显微镜检查(81.8%)更具敏感性,其特异性为99.7%. 因此,抗原捕获法-ELISA试剂盒对于贾第虫感染的一次粪便样本的阳性诊断率较高,而在一次粪便显微镜检查结果阴性时并不能排除贾第虫感染的可能性,故增加粪便显微镜检查的次数(至少3次)方可提高阳性诊断率^[26]. 但是,由于ELISA试剂盒不能检测出潜在病原体,因此他并不能取代寄生虫显微镜检查.

1.2 检测抗体

1.2.1 IgG 检测血清中的特异性IgG抗体可作为辅助诊断方法^[27]. 用ELISA法和间接免疫荧光抗体法检测巴西日托中心147名0-6岁年龄组的儿童的滤纸血样和每名儿童的三份粪便样本(每份粪便样本独立包装,并经自然沉淀法和硫酸锌漂浮法处理),其中,93名儿童的粪便样本查到贾第虫包裹. ELISA法在100(68%)份血清样本中测得抗贾第虫IgG抗体(其中粪检阳性病例为67,粪检阴性病例为33),间接免疫荧光抗体法在93(63.3%)份血清样本中测得抗贾第虫IgG抗体(其中粪检阳性病例为76,粪检阴性病例为17). ELISA法和间接荧光抗体法检测贾第虫抗体的敏感性分别为72%和82%,而间接荧光抗体法的特异性(70%)强于ELISA法(39%). 对于三份粪检贾第虫包裹均阴性的儿童,ELISA法有一定的假阳性率^[28]. 在贾第虫病的流行区内,对于那些无临床表现的大部分患者,间接荧光抗体法的检出率较ELISA法高,与显微镜检查结果相符,与十二指肠引流液检查的符合率可达100%,此法一般只适用于个例的诊断,不能替代病原检查;而ELISA法一般只作为临床辅助诊断,更适宜于流行病学调查^[29].

1.2.2 IgA 应用ELISA法检测患者唾液内特异性抗贾第虫IgA抗体也可作为一种诊断贾第虫感染的筛选方法^[30-32]. 对36名以腹泻为主要症状的埃及患者粪便样本同时进行直接涂片检查和十二指肠引流液检查,其中94.4%粪检贾第虫阳性患者的唾液内可测得特异性的抗贾第虫IgA抗体,33.3%粪检贾第虫阴性患者的唾液内可测得特异性的抗贾第虫IgA抗体. 十二指肠引流液检查为

阴性患者的唾液内均未测得特异性的抗贾第虫IgA抗体^[33]. 对于有长期(>1 mo)持续症状的患者, ELISA法检测特异性的抗贾第虫IgA抗体适用于贾第虫病的普查^[34-35].

2 免疫荧光抗体测定法 (IFA)

2.1 直接荧光抗体测定法(DFA) 为了确定贾第虫病的发病率和临床特点, Morimoto *et al*^[36]用直接涂片显微镜法、直接荧光抗体测定法和Kohn's一步染色法检测了Kochi医学院附属医院1790名患者的粪便, 17(0.95%)名患者的粪便中测得贾第虫包囊. 这些患者多为中老年群体(41-79岁), 并且大多数(除外2例)无海外旅游史. 因此, 寄生虫感染的诊断更多依靠实验室粪便的检查, 以排除可引起感染的寄生虫包囊携带者^[37-39].

直接荧光抗体测定法对保存在5℃的冷藏室中的14份粪便样本, 保存在零下20℃的冰箱中9份粪便样本, 保存在常温3.9%甲醛溶液(formalin-saline solution)中28份粪便样本中的贾第虫包囊均可测得. 而直接涂片法检测到在冰箱中保存的粪便样本中的贾第虫包囊的阳性率为56%, 检测到冰冻粪便样本中的贾第虫包囊的阳性率为93%, 检测保存超过24 mo粪便样本中的贾第虫包囊为阴性^[40]. 直接荧光抗体测定法检测长期保存的粪便样本中的贾第虫包囊是一种有效的方法^[41-43].

2.2 免疫磁性分离法-间接荧光抗体测定法(IMS-IFA) 近年来出现了一些新的检查方法, Souza *et al*首次报道了IMS-IFA检测人体粪便中贾第虫包囊, FAUST *et al*和Lutz寄生虫学检验技术的检测结果作为对照^[44]. 粪便样本固定在醋酸钠醋酸甲醛(formalin-sodium acetate-acetic acid, SAF)溶液中, 室温20℃保存不超过4 mo. 对127份粪便样本检测结果为, IMS-IFA检测贾第虫包囊的阳性检出率为27.5%, FAUST和Lutz寄生虫学检验技术检测贾第虫包囊的阳性检出率为15.7%. IMS-IFA较FAUST和Lutz寄生虫学检验技术检测粪便中贾第虫包囊具有更高灵敏度. IMS-IFA可同时检测多份粪便样本, 缩短样本保存的时间, 并可增加贾第虫包囊的回收率^[45].

3 酶免疫测定法(EIA)

EIA试剂盒可用于检测粪便样本中贾第虫和溶组织内阿米巴原虫^[46-47]. Schunk *et al*^[48]从德国慕尼黑大学附属医院门诊患者收集了276份粪

便样本, 以显微镜检查的结果作为参考标准时, EIA试剂盒检测贾第虫的敏感性为100%、特异性为99.6%, 检测溶组织内阿米巴原虫的敏感性为81.8%、特异性为99.2%. 两种检查方法与其他肠道内寄生原虫无交叉反应^[48-49]. 由于其他潜在病原体的存在, 所以该法并不可以取代显微镜检法, 但EIA试剂盒可能会成为一种非常有效且有价值的诊断辅助方法^[50-52].

实际上, 对于无症状的贾第虫感染者和个别有阳性体征贾第虫感染的患者EIA试剂盒的敏感性差别不大(77/83%). 无论对于有贾第虫感染阳性体征的患者(83/75%), 无症状地感染贾第虫的患者(77/61%), 还是对总体(80/67%)来说, 使用EIA试剂盒检测单份粪便样本的敏感性均较高^[53]. 为了使贾第虫感染诊断的敏感性大于90%, 常规寄生虫学检查和EIA试剂盒并用是必要的^[54-56].

4 试剂盒

目前已有不少检测蓝氏贾第虫的诊断试剂盒供市售. 由于在蓝氏贾第虫感染流行的地区, 常伴有诸如溶组织内阿米巴、隐孢子虫等肠道原虫的感染, 因而研究者和生产厂商常将诊断试剂盒设计成可同时诊断多种肠道原虫感染.

4.1 贾第虫/隐孢子虫快速检测试剂盒(Color PAC) 全称Color PAC复合快速固相定性免疫层析实验(Color PAC combination rapid solid-phase qualitative immunochromatographic assay), 为美国Becton Dickinson公司产品, 可同时检测蓝氏贾第虫和隐孢子虫的感染, 完成整个实验约需10 min. 检测蓝氏贾第虫的敏感性和特异性均为100%, 检测隐孢子虫的敏感性和特异性分别为97.6%和100%^[57]. Color PAC快速检测试剂盒虽然不能替代常规粪便中虫卵和寄生虫的检查, 但在蓝氏贾第虫和隐孢子虫感染的确诊中是非常有用的.

4.2 贾第虫/隐孢子虫微量检测试剂盒(ProSpecT) ProSpecT Giardia/Cryptosporidium Microplate Assay系美国Alexon公司生产, 可同时检测蓝氏贾第虫和隐孢子虫, 检测蓝氏贾第虫的敏感性和特异性分别为94%和100%, 检测隐孢子虫的敏感性和特异性分别为97%和100%^[58-61]. 当被检测的粪便样本中有血时, ProSpecT试剂盒有一定的假阳性率^[62-63].

4.3 Color PAC与ProSpecT比较 应用Color PAC试剂盒检测241份粪便样本, 贾第虫感染阳性

■应用要点

本文对每一种免疫学诊断方法进行细致的评价, 以便对不同的发病群体、不同的卫生环境使用比较灵敏的检查方法.

者53例, 隐孢子虫感染阳性者90例. ProSpecT试剂盒检测56例贾第虫感染阳性者, 93例隐孢子虫感染阳性者. 两种试剂盒检测贾第虫感染阳性符合率为98.7%, 隐孢子虫感染阳性符合率为98.1%^[64-65]. 在使用中Color PAC试剂盒较ProSpecT试剂盒更简便、快速, 但价格较高^[66-67].

4.4 寄生虫酶免疫测定筛选膜(Triage) 全称为Triage寄生虫膜上酶免疫(triage parasite panel enzyme immunoassay), 是一种新的定性酶免疫测定方法, 由美国BIOSITE Diagnostics公司生产. 原理为用已知的抗体捕获特定抗原并固定在膜上, 完成每人份粪便样本的检测约需15 min^[68]. 值得注意的是Triage试剂盒所需的粪样必须是新鲜粪便及其立即冻存者, 否则影响结果的判读. 检测444份粪便样本, 贾第虫感染阳性170例, 敏感性和特异性分别为95.9%和97.4%, 阴性预测值(NPV)为97.4%; 溶组织内阿米巴/迪斯帕内阿米巴感染阳性99例, 敏感性和特异性分别为96.0%和99.1%, 阴性预测值(NPV)为98.8%; 微小隐孢子虫感染阳性60例, 敏感性和特异性分别为98.3%和99.7%, 阴性预测值(NPV)为99.7%^[69]. 在粪样中同时检测贾第虫、溶组织内阿米巴/迪斯帕内阿米巴、微小隐孢子虫感染时, Triage试剂盒是一种简便、可供选择的方法^[68].

4.5 贾第虫/隐孢子虫免疫快速检测卡(ImmunoCard STAT) ImmunoCard STAT Cryptosporidium/Giardia rapid assay实质上是使用快速固相定性免疫层析法同时检测蓝氏贾第虫和隐孢子虫, 产于美国Meridian Bioscience的一种试剂盒, 要求在12 min内完成对未经浓缩固定在甲醛溶液中每份粪便样本的检测. 检测170份已知贾第虫阳性标本结果为159份, 敏感性和特异性分别为93.5%和100%, 阳性预测值(PPV)为100%, 阴性预测值(NPV)为95.5%, 感染数量较少(免疫荧光测定法仅见10-100个包裹)的7份粪便样本和3份仅有滋养体的粪便样本呈假阴性, 但1份呈假阴性的粪便样本却含有大量包裹. 感染数量较少的粪便样本呈现假阴性说明该试剂盒的敏感性受到一定的限制, 却无法解释含有大量包裹的呈假阴性粪便样本反复检测仍呈假阴性的结果, 该作者认为这份粪便样本在固定前经过了不适的处理或使用了不适的固定液^[70].

总之, 贾第虫病的首选诊断方法仍是粪便涂片检查. ELISA法适于贾第虫病的血清流行病学调查、疗效考核及防治结果的检测. DFA可以检

测到在不同环境保存且已发生形状改变的粪便样本中的贾第虫包裹. IFA操作简便, 可用于特异性抗原的检查与定位. 试剂盒可同时检测贾第虫等其他肠道原虫的感染, 也可对水源及其他污染源进行筛查. 贾第虫病的免疫学诊断方法较多, 而且其敏感性和特异性均较高, 对贾第虫病的临床诊断、治疗、预后带来了极大的方便.

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