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文献综述 REVIEW

IGRA及TB-PCR在肠结核与克罗恩病鉴别诊断中的价值

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Value of interferon-γ release assay and polymerase chain reaction for *Mycobacterium tuberculosis* in differentiation of intestinal tuberculosis from Crohn's disease

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Abstract
China is one of the countries having the highest burden of tuberculosis. The number of patients with Crohn's disease (CD) is gradually increasing in China. Sometimes intestinal tuberculosis (ITB) and CD are quite similar in clinical manifestations and the findings of radiological and endoscopic examinations, and it is difficult to differentiate the two diseases; however, the treatments and prognosis of the two diseases are completely different. Besides clinical characteristics, radiological examinations, endoscopic examinations, histopathological examinations, acid-fast staining, *Mycobacterium tuberculosis* culture, serum markers and tuberculin skin test (TST), interferon-γ release assay (IGRA) and polymerase chain reaction for *Mycobacterium tuberculosis* (TB-PCR) have recently been used to differentiate ITD from CD. Both IGRA and TB-PCR have a high sensitivity and specificity in diagnosis of ITB when differentiating ITB from CD. This review focuses on the value of IGRA and TB-PCR in the differentiation of ITB from CD.

Key Words: Interferon-γ release assay; Polymerase chain reaction for *Mycobacterium tuberculosis*; Intestinal tuberculosis; Crohn's disease; Differential diagnosis

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摘要
中国是结核病高负担国家之一, 加之目前我国克罗恩病(Crohn's disease, CD)患者数量在逐步增加, 而肠结核(intestinal tuberculosis, ITB)和CD的临床表现、放射学检查及内镜检查结果等方面有时很相似. 两者的鉴别有时很困难, 然而两者的治疗方案及预后截然不同. 除了从传统的临床表现、放射学检查、内镜检查、组织病理学检查、抗酸染色、结核分枝杆菌培养、血清标志物及结核菌素皮肤试验(tuberculin skin test, TST)等方面鉴别这两种疾病, 近年来的研究用γ干扰素释放分析(interferon-γ release assay, IGRA)及结核分枝杆菌聚合酶链反应(polymerase chain reaction for *Mycobacterium tuberculosis*, TB-PCR)来鉴别ITB与CD. 在鉴别ITB和CD时, IGRA及TB-PCR诊断ITB的敏感度及特异度均较高. 本文就IGRA与TB-PCR在鉴别ITB和CD中的价值进行综述.

关键词: γ干扰素释放分析; 结核分枝杆菌聚合酶链反应; 肠结核; 克罗恩病; 鉴别诊断

核心提示: 肠结核(intestinal tuberculosis, ITB)临床

■背景资料
目前我国结核病年发病约为130万例, 占全球发病的14.3%, 位居全球第2位. 肠结核(intestinal tuberculosis, ITB)属于结核病的一种类型, 我国近十多年来克罗恩病(Crohn's disease, CD)就诊人数呈逐步增加的趋势非常明显, 而ITB临床上与CD酷似, 而治疗方法完全不同, 两病的鉴别一直是个难题.

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上与克罗恩病(Crohn's disease, CD)酷似, 两病的鉴别一直是我们所面对目前难题. 传统的鉴别方法在鉴别ITB与CD时具有诸多局限性, 而近年来的研究用γ干扰素释放分析(interferon-γ release assay, IGRA)及结核分枝杆菌聚合酶链反应(polymerase chain reaction for *Mycobacterium tuberculosis*,TB-PCR)来鉴别ITB与CD. 结果显示IGRA及TB-PCR诊断ITB的敏感度及特异度均较高, 这为两病的鉴别提供了有价值的新方法, 两病的鉴别是目前及今后相当长时间内的研究热点.

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■相关报道
Kim等报道肠结核组γ干扰素释放分析(interferon-γ release assay, IGRA)阳性率较克罗恩病组高, 差异具有统计意义, 且诊断ITB的敏感度为67%, 特异度为90%. 而Ramadass等研究报道粪便TB-PCR诊断ITB的敏感度为79%, 特异度为88%. 研究结果显示IGRA及TB-PCR诊断ITB的敏感度及特异度均较高.

0 引言

我国是全球22个结核病流行严重的国家之一, 目前我国结核病年发病人数约为130万, 占全球发病的14.3%, 位居全球第2位[1]. 发展中国家是结核病的高发区, 肠结核(intestinal tuberculosis, ITB)是常见的肺外结核病[2]. 肺外结核占全球所有结核病的15%-20%[3], 欧盟国家肺外结核占所有结核病的比例从2002年的16.4%上升到2011年的22.4%[4]. ITB是结核分枝杆菌引起的肠道慢性特异性感染. 克罗恩病(Crohn's disease, CD)是一种病因尚不十分清楚的胃肠道慢性炎性肉芽肿性疾病[5]. 研究表明CD在欧美国家是常见病[6-9], CD属于炎症性肠病的一种类型, 发展中国家炎症性肠病的发病率呈上升趋势[10]. Prideaux等[11]报道近20年来, 亚洲国家炎症性肠病发病率和患病率呈逐年增加趋势. 在我国, 近十多年来CD就诊人数呈逐步增加的趋势非常明显[12], 并且CD存在东西方差异[13]. CD的临床表现缺乏特异性, 极易导致误诊[14]. 何瑶等[15]进行的回结肠CD与ITB临床及内镜特征比较研究发现半数患者不能依靠活检病理和临床内镜评分获得比较可靠的诊断. 传统的鉴别方法在鉴别ITB与CD时具有诸多局限性. ITB临床上与CD酷似, 而治疗方法完全不同, 两病的鉴别一直是个难题[16]. 近年来的研究用γ干扰素释放分析(interferon-γ release assay, IGRA)及结核分枝杆菌聚合酶链反应(polymerase chain reaction for *Mycobacterium tuberculosis*, TB-PCR)来鉴别ITB与CD. 在鉴别ITB与CD时, IGRA及TB-PCR诊断ITB的敏感度及特异度均较高, 提示有较好的应用价值及应用前景.

1 IGRA在ITB与CD鉴别诊断中的价值

研究表明结核分枝杆菌(*mycobacterium tuberculosis*, *MTB*)基因中含有*RD1*基因序列, 该序列编码产生的培养滤液蛋白-10(culture filtrate protein-10, CFP-10)和早期分泌靶向抗原-6(early secretory antigenic target-6, ESAT-6)是MTB的特异性抗原[17]. 当MTB的特异性抗原再次刺激感染MTB后的记忆性T淋巴细胞, 记忆性T淋巴细胞就会释放γ干扰素, IGRA通过检测γ干扰素的分泌情况来诊断有无MTB感染[18]. 近年来国外的研究表明IGRA在检测MTB感染中有较好的敏感度和特异度[19-22]. 目前应用在ITB与CD鉴别诊断中的IGRA包括QuantiFERON-TB gold test(QFT-G)和结核杆菌T细胞斑点试验(T cell spot of tuberculosis test, T-SPOT.TB).

1.1 QFT-G QFT-G利用MTB特异性蛋白质ESAT-6和CFP-10刺激宿主全血中的淋巴细胞, 如果宿主曾经暴露于MTB, 暴露于MTB后的致敏淋巴细胞经ESAT-6和CFP-10再次刺激就会释放γ干扰素, 然后用酶联免疫吸附试验检测释放的γ干扰素来诊断有无MTB感染. 卡介苗及环境分枝杆菌可能导致TST出现假阳性结果, 而不能导致QFT-G出现假阳性结果, 所以QFT-G特异度比TST更好, 美国FDA已批准用QFT-G作为一种辅助检查来诊断结核病和结核的潜伏期[23,24]. Klein等[25]研究报道在行抗肿瘤坏死因子-α治疗的患者中检测潜伏期结核QFT-G的特异度比TST更好. Khalil等[26]研究得出检测活动性肺结核时QFT-G的敏感度比TST更好, 且其敏感度不受之前接种过卡介苗及暴露过环境分枝杆菌的影响. ITB属于肺外结核病, Fan等[27]进行的Meta分析得出QFT-G诊断肺外结核的总敏感度和特异度分别为72%(95%CI: 65%-79%)和82%(95%CI: 78%-87%). Kim等[28]研究报道ITB组QFT-G阳性率为66.7%, CD组QFT-G阳性率为9.7%, ITB组QFT-G阳性率较CD组高, 差异具有统计学意义; 对于抗酿酒酵母抗体(anti-saccharomyces cerevisiae antibodies, ASCA)阳性或QFT-G阴性的病例, ASCA诊断CD的敏感度为44.4%、特异度为96%、阳性预测值为91.4%、阴性预测值为64.3%. 在ITB很普遍的韩国, ASCA是一种有价值的诊断CD的方法, 尤其将ASCA与QFT-G联合起来用于鉴别CD与ITB时, 这种联合诊断法可能在CD与ITB的鉴别诊断中非常有用. 另外, Kim等[29]研究发现QFT-G与TST有很好的一致性, ITB组的QFT-G阳性率(67%)较

CD组阳性率(9%)高, 差异具有统计学意义; ITB组的TST阳性率(67%)较CD组阳性率(16%)高, 差异具有统计学意义. QFT-G诊断ITB的敏感度为67%, 特异度为90%, 阳性预测值为87%, 阴性预测值为73%, 虽然QFT-G具有一定的局限性, 但QFT-G结合TST在诊断ITB时的效能是令人满意的. 目前QFT-G用于鉴别ITB与CD的研究较T-SPOT.TB用于鉴别ITB与CD的研究少, 待今后进一步研究来证实QFT-G在ITB与CD鉴别诊断中的价值.

1.2 T-SPOT.TB T-SPOT.TB是应用酶联免疫斑点技术检测经MTB特异性抗原ESAT-6和CFP-10刺激后外周血中释放γ干扰素的T细胞[30]. TST中使用的纯蛋白衍化物的某些抗原成分与卡介苗和环境分枝杆菌的抗原成分相同, 可发生交叉反应, 导致TST的特异性较低; 并且TST对于免疫受损患者的敏感度较低[31]. 国外报道T-SPOT.TB诊断结核的敏感度为83%-97%[32]. Feng等[33]研究报道T-SPOT.TB诊断结核病的敏感度及特异度均较TST更好. Meier等[34]研究报道在确诊为结核病的72例患者中有70例T-SPOT.TB呈阳性, T-SPOT.TB诊断结核的敏感度为97.2%. 并对其中45例T-SPOT.TB阳性患者行TST, 发现TST的阳性率为89%, 对这45例T-SPOT.TB阳性患者而言, T-SPOT.TB的阳性率(100%)与TST的阳性率(89%)的差异无统计学意义. ITB属于肺外结核病, Liao等[35]研究报道T-SPOT.TB诊断肺外结核的敏感度和特异度分别为79.8%和81.6%. Fan等[27]的Meta分析得出T-SPOT.TB诊断肺外结核的总敏感度和特异度分别为90%(95%CI: 86%-93%)和68%(95%CI: 64%-73%). Baek等[36]研究得出T-SPOT.TB诊断ITB的敏感度为100%、特异度为78.1%、阳性预测值为68.9%、阴性预测值为100%, 当ITB与CD的鉴别有困难时, T-SPOT.TB的鉴别诊断价值较高: 阴性结果可基本排除ITB. Li等[37]研究得出T-SPOT.TB诊断ITB的敏感度为84.2%, 特异度为75.4%, 阳性预测值为50.0%, 阴性预测值为94.2%; 在结核流行地区鉴别ITB和CD时, 鉴于T-SPOT.TB有很高的阴性预测值可很好地排除ITB, 所以他可能是一种在实践中有价值的诊断方法. Lee等[38]研究报道T-SPOT.TB诊断ITB的敏感度为100%、特异度为83.3%、阳性预测值为60.0%、阴性预测值为100%, 当鉴别ITB与CD有困难时, T-SPOT.TB可能是一种可快速排除ITB的有用方法. Lei等[39]研究得出T-SPOT.TB诊断ITB的敏感度为86%、特异度为93%、阳性预测值为88%、阴性预测值为91%, 由于T-SPOT.TB在诊断ITB时具有很高的特异性及阴性预测值, 其在排除ITB时具有较高的价值. 雷少妮等[40]研究报道CD组、ITB组、肠外结核组及其他疾病组T-SPOT.TB阳性率分别为6.7%、85.7%、70%及0%, 各组间差异具有统计学意义; T-SPOT.TB检测ITB的敏感度为85.7%、特异度为93.3%, 阴性预测值为12.5%.

2 TB-PCR在ITB与CD鉴别诊断中的价值

PCR可使DNA的合成量呈指数增长, 可用PCR检测MTB DNA, TB-PCR是一种在鉴别ITB及CD时的快速病原学诊断方法. 在目前的研究中, TB-PCR的引物来自MTB的特异性IS6110序列, IS6110序列具有较高的敏感性和特异性[41]. 目前TB-PCR可用于肠黏膜组织和粪便中的MTB DNA检测.

2.1 粪便MTB DNA检测 Ramadass等[42]研究得出结核在印度很普遍, 在鉴别ITB与CD时, 从确诊为ITB或CD患者的粪便中提取DNA, 并实施TB-PCR, 粪便TB-PCR诊断ITB的敏感度为79%, 特异度为88%, 阳性预测值为79%, 阴性预测值为88%. Balamurugan等[43]研究报道12例已确诊ITB患者中有11例粪便TB-PCR阳性, 而15例健康对照者的粪便TB-PCR全为阴性, ITB组和健康对照组TB-PCR阳性率的差异具有统计学意义并且粪便TB-PCR的敏感度优于病理检查及肠黏膜组织MTB培养. Sucharita等[44]对27例未治疗的ITB及48例CD实施粪便TB-PCR, ITB组TB-PCR阳性率为77.8%, CD组TB-PCR阳性率为14.6%, 差异具有统计学意义; TB-PCR的敏感度、特异度、阳性预测值及阴性预测值分别为75%、87%、77%及85%. Balamurugan等[45]研究报道粪便TB-PCR阳性率在未治疗的ITB组、治疗过的ITB组、痰涂片阳性肺结核组及对照组分别为88.8%(16/18)、0%(0/8)、85.7%(12/14)及0%(0/30); 粪便TB-PCR诊断ITB的敏感度、特异度、阳性预测值及阴性预测值分别为88.8%、100%、100%及93.7%.

2.2 肠黏膜组织MTB DNA检测 1994年Anand等[46]对1例慢性腹泻患者的肠黏膜组织实施TB-PCR, 与MTB探针杂交结果呈阳性, 该患者在抗结核治疗后内镜下异常病变完全消失, 该研究表明在诊断ITB时可对肠黏膜活检组织行TB-PCR. 甘华田等[47]对36例ITB肠黏膜组织及26例CD

■创新盘点

本文详细而全面介绍从细胞免疫方面及生物分子水平来鉴别肠结核及克罗恩病.

■应用要点
本文着重综述IGRA及TB-PCR在肠结核与克罗恩病鉴别诊断中的价值, IGRA从细胞免疫方面及TB-PCR从病原学方面为解决肠结核及克罗恩病的鉴别难题开辟了一条新的途径.

肠黏膜组织实施TB-PCR发现ITB组及CD组的TB-PCR阳性率分别为75%和0%. Jin等[48]认为病理组织学检查与TB-PCR联用是鉴别诊断CD与ITB的最佳方法, 对确诊为ITB或CD的患者进行病理组织研究, 并实施TB-PCR, TB-PCR诊断ITB的敏感度和特异度分别为88.9%和100%; 发现病理特征结合了组织TB-PCR后, 依据病理特征诊断ITB的敏感度可显著提高. Amarapurkar等[49]进行了一项超过3年的前瞻性研究发现: 与ITB鉴别时, 发热、便血、腹泻和病程在诊断CD时的准确度最高, 其准确度为84.62%; 而对活检组织实施TB-PCR的准确度为82.6%. 陈瑜君等[50]研究得出TB-PCR在ITB与CD的鉴别诊断中, TB-PCR诊断ITB的敏感度为32%, 特异度为100%, 阳性预测值为100%, 阴性预测值为59.5%. 甘华田等[51]研究得出TB-PCR检测MTB DNA在ITB组的总阳性率为63.2%, 在与CD肉芽肿形态相同的ITB组中的阳性率为71.4%, 在无肉芽肿病变的ITB组中的阳性率为64.7%, 在CD组全为阴性; 而抗酸染色在ITB组总阳性率为21.1%, TB-PCR在ITB组的总阳性率较抗酸染色高, 差异具有统计学意义, 该研究得出内镜活检病理对肠结核与CD的鉴别诊断有一定局限, PCR技术是鉴别ITB和CD极有价值的一种新方法. Amarapurkar等[52]研究报道肠黏膜组织TB-PCR在ITB组的阳性率仅21.6%, 在CD组的阳性率为5%, TB-PCR诊断ITB的特异性达95%, 故TB-PCR在ITB与CD的鉴别诊断中可能有价值.

3 结论

我国是结核病高发国家之一, 且我国CD的发病率呈增高趋势, 然而ITB和CD在许多方面极为相似, 有时两者的鉴别非常困难, 然而两者的治疗及预后截然不同, 误诊率非常高, 错误的治疗甚至可能危及患者的生命, 传统的鉴别方法具有诸多局限性. 在ITB和CD的鉴别诊断中, IGRA诊断ITB的敏感度及特异度均较高, 尤其较高的阴性预测值可快速排除ITB, 且IGRA具有不受卡介苗及环境分枝杆菌的影响, 结果客观, 非侵入性及方便快捷等优点; 在ITB和CD的鉴别诊断中, TB-PCR诊断ITB的敏感度及特异度均较高, 尤其极高的特异度在临床诊断中有极好的应用价值及应用前景, 已有的研究表明通过控制主客观因素可减少TB-PCR的假阳性及假阴性结果, 并且可提高TB-PCR敏感度. TB-PCR出结果快, 尤其粪便TB-PCR具有方便检测及非侵入性等优点, 但是TB-PCR技术要求高. 希望今后寻找到除了MTB的特异性IS6110序列以外MTB的其他特异性序列以提高TB-PCR的敏感性. 虽然传统的鉴别ITB与CD的方法具有诸多局限性, 但其具有费用低、技术要求不高等优点, IGRA、TB-PCR及某些传统方法的结合可能提高诊断的效能而并不大大增加医疗费用. 希望今后进行大样本量的前瞻性研究以评价IGRA和TB-PCR在鉴别ITB和CD中的价值.

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■同行评价
本文就IGRA与TB-PCR在鉴别ITB和CD中的价值进行综述, 思路清楚, 资料较完整, 对临床有一定参考价值.

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