TURKISH INFLAMMATORY BOWEL DISEASE SOCIETY RECOMMENDATIONS ON SELECTED TOPICS OF CROHN'S DISEASE

TÜRK İNFLAMATUVAR BARSAK HASTALIKLARI DERNEĞİNİN CROHN HASTALIĞI İLE İLGİLİ SEÇİLMİŞ KONULARDA ÖNERİLERİ

What is the most accurate method for the diagnosis of intestinal tuberculosis?

İntestinal tüberkülozun tanısında en doğru yöntem nedir?

Key words: Intestinal tuberculosis, diagnosis

Anahtar kelimeler: Barsak tüberkülozu, tanı

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INTRODUCTION

Tuberculosis infection is very old in the history of humanity, which complicates the diagnosis and treatment of inflammatory bowel diseases. Although it is rare in the developed countries, intestinal tuberculosis is a prevalent disease in the developing countries. It is life threatening, if not diagnosed. Since the symptoms are non-specific, high index of suspicion is important for diagnosis. Intestinal tuberculosis is diagnosed through clinical presentations (abdominal pain, fever, diarrhea, anemia, high sedimentation rate), radiologic imaging, colonoscopy, tissue biopsy (caseous granuloma) microbiologic assessments (ARB, culture) and PCR. ARB, culture positivity and the presentation of caseous granuloma are essential for the diagnosis. However, there are a few data in terms of the diagnosis of intestinal tuberculosis through PPD and IGRA, therefore further studies are needed. Quantiferon Tb-Gold and Elispot are two different IGRA tests in commercial use.

METHODS

Systematic literature search was carried out in Medline using the following key words: Intestinal tuberculosis AND diagnosis, intestinal tuberculosis AND PCR (ARB OR pathology OR tissue culture OR endoscopic finding), intestinal tuberculosis AND biopsy number, intestinal tuberculosis, intestinal tuberculosis AND tissue culture, intestinal tuberculosis AND PCR (MeSH), Quantiferon, Tuberculosis AND PPD not case report, tuberculosis (MeSH) AND PPD, PPD AND Quantiferon. All of the studies performed in adults were evaluated. Moreover, screening the referred literature, other studies were obtained.

After 3e searching of 1240 articles regarding the methods used in the diagnosis of intestinal tuberculosis and tuberculosis sixty one studies were retrieved . The sensitivity and specificity of the diagnostic methods, comparative methods and the essential methods for diagnosis were determined in the evaluation of the studies. The types of the 61 studies were demonstrated in Table 1, and the distribution of the methods evaluated in the studies, in Table 2.

Table 1. The types of the studies analyzed

Type of the study	Number of studies
Meta analysis	1
Randomized control	17
Prospective study	42
Review	1

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Table 2. The distribution of the diagnostic methods in the studies analyzed

The distribution of diagnostic methods	The number of studies
Number of biopsies	13
Tissue culture	6
PCR	6
Quantiferon	15
PPD	10

RESULTS

The Numbers of the Biopsies

The number of colonoscopic biopsies from intestinal tuberculosis varies between 2 to 10 in different series. The higher the number of biopsies, the higher is the positivity of ARB and PCR in the tissues (1-13).

Tissue Culture

Tissue culture takes a long time (3-8 weeks) and its sensitivity is low. The studies on tissue culture are in case series. The sensitivity of tissue culture in the diagnosis of intestinal tbc is between 21% and 54.5% and the specificity is 100% (2,6, 10,13,14). The sensitivities of tissue culture, PPD and histopathology in twenty nine cases with intestinal tuberculosis were found to be 40%, 86% and 41%, respectively (6).

In another case series comparing 26 patients with Crohn's disease and 26 patients with intestinal tuberculosis, the tissue culture sensitivity was between 25% to 35% and the specificity was 100%, the PCR sensitivity was 65.4 and the sensitivity of caseification necrosis was 34.6% (13).

As it was reported by Leung et al., tissue culture sensitivity and ARB positivity were 21% and 84%, respectively, while the sensitivity of caseification necrosis was 84%, in a case series with 19 intestinal tuberculosis (14).

ARB

Unfortunately, demonstration of ARB in the tissues is one of the methods with low sensitivity in the diagnosis of intestinal tuberculosis. Gan et al. re-

Table 3. The analyzed results regarding the number of biopsies in the diagnosis of intestinal tbc

Author	Year	Journal	Recommended number of biopsies
Dinesh K. Bhargava	1985	Gastrointestinal Endoscopy	8-10
Shigeru Sato	2004	Gastrointestinal Endoscopy	4-6
Karen D	1998	The American Journal of Gastroenterology	8-10
Kyoung Mee Kim	1998	The American Journal of Gastroenterology	2-8
Das	2000	JAPI	6-8
Dineash K. Bhargava	1992	Gastrointestinal Endoscopy	8-10
S. P. Misra	2004	Endoscopy	8-10
R. Kirsch	2006	J Clin Pathol	4-
S Shah	1992	Gut	6-8
Majid Abdulrahman Almadi	2008	The American Journal of Gastroenterology	≥6
Anna B Pulimood	2005	Journal of Gastroenterology and Hepatology	5-6
Anna B Pulimood	1999	Gut	5-6
Deepak N Amarapurkar	2008	World J Gastroenterol	≥6

Table 4. The analyzed results regarding tissue culture in the diagnosis of intestinal tuberculosis

Author	Year	Journal	The sensitivity of tissue culture	Specificity	Comparator method	Gold standard
Bhargava DK	1985	J Trop Med Hyg	42%	-	-	-
Shigeru	2004	Gastrointestinal Endoscopy	54.5%	-	-	-
Dinesh K. Bhargava	1992	Gastrointestinal Endoscopy	40%	-	PPD (Sen 86%) Histology (Sen 41%)	-
Majid Abdulrahman Almadi	2008	Clinical Reviews	25-35%	-	-	-
Deepak N Amarapurkar	2008	World Journal of Gastroenterol	23.1%	100%	PVR (Sen 65.4%), Caseification (Sen 34.6%)	-
VKS Leung	2006	Hong Kong Med J	21%	-	ARB (Sen 84%), Caseification necrosis (Sen 42%)	-

ported the ARB sensitivity as 44% and the PCR sensitivity as 75% in a case series including 36 patients with intestinal tuberculosis. In various case series including patients with intestinal tuberculosis, the ARB sensitivities in the tissue were 8%, 20.5%, 44% and 88% while the specificities were 100% (14, 16-18).

PCR

The sensitivity and specificity of PCR may be up to 82.6% and 95%, respectively. Another advantage of the tissue PCR is that the results can be obtained rapidly (10). In a series of 36 patients with intestinal tuberculosis and 26 patients with Crohn's disease, the PCR sensitivity was 75% and specificity was 100%, and the ARB sensitivity was 44% and specificity was 100% in the diagnosis of intestinal tuberculosis (15). In a relatively larger case series including 60 patients with intestinal tuberculosis and 20 patients with Crohn's disease, the PCR specifity was 95%, while the sensitivity remained up to 21.6% (19). Ramadass et al. demonstrated fecal PCR sensitivity and specifity as 88% and 100%, respectively (20). In a series of 20 patients with intestinal tuberculosis and 20 patients with Crohn's disease, PCR sensitivity was 30%, and specifity was 95%, and the sensitivity and specifity for demonstrations of ARB and caseification necrosis were 45% and 100%, respectively, in the diagnosis of intestinal tuberculosis (21). In another case series including 39 patients with intestinal tuberculosis and 30 patients with Crohn's disease, it was reported that the PCR sensitivity was 64.1% and the specifity was 100%, the ARB sensitivity was 20.5% and the specifity was 100%, and the caseification necrosis sensitivity was 17.9 and specifity was 100%, in the diagnosis of intestinal tuberculosis (17).

PPD-IGRA

a. (PPD-IGRA) in tbc

In view of the fact that there are very few articles concerning the use of PPD and IGRA (interferon

Table 5. The analyzed results regarding PCR in the diagnosis of intestinal tuberculosis

Author, year, journal	PCR sensitivity	PCR specifity	Comparator method	Gold standard
Gan Huatian 1994 Chinese Medical Journal	75%	100%	ARB (Sen 44%, Spec 100%)	-
DN Amar. 2004 JAPI	21.6%	95%	-	ARB, tissue culture, caseous granuloma
D Hillemann 2005 Int J Tuberc Lung Dis	66.6%	100%	ARB (Sen 8%, Spec 100%)	-
Ramadass Balamurugan 2006 Jour Of Clin Microbiology	88% (Fecal PCR)	100% (Fecal PCR)	-	-
Anna B. Pulimood 2008 Am J Clin Pathol	30%	95%	ARB Bx (caseous granuloma) (Sen 45%, Spec 100%)	-
Hua Tian Gan 2002 The American Journal Of Gastroenterology	64.1%	100%	ARB (Sen 20.5%, Spec 100%), (caseous granuloma) (Sen 17.9%, Spec 100%)	-

Table 6. The analyzed results regarding the PPD test in the diagnosis of active tbc

Author/year/ Journal	The risk group	Country	n	Sensitivity (%)	Specificity (%)	PPD-/Quan– (%)	PPD-/Quan+ (%)
Irini Gerogianni, 2008, Respirology	Greek population	Greece	191	BCG+: 60.2% BCG-:44% 74%: active tbc	-	-	-
Öznur Ak, 2009 Jpn J Infect Dis	Pulmonary, extra pulmonary tbc	Turkey	65	68.2% (pulmonary tbc), 62% (extra pulmonary tbc)	-	6-40%	9-60%
V Bartu, 2008 The Journal of International Medical Research	Tbc	Prague	53	62%	-	8%	26%
Soysal 2008 Int J Tuberc Lung Dis	Active pulmonary tbc	Turkey	100 tbc, 47 healthy	70% (PPD≥10 mm)	%35	-	-

Table 7. The analyzed results regarding the IGRA test in the diagnosis of active tbc

Author/year/ journal	The risk group	Country	n	Sensitivity (%)	Specificity (%)	PPD-/Quan– (%)	PPD-/Quan+ (%)
Irini Gerogianni 2008, Respirology	Greek population	Greece	191	BCG(+): 27.5% BCG (-): 41.9% 85.1%(active tbc)	-	-	-
Kazue Higuchi 2008 Tuberculosis	Contaminated with Tbc	Japan	172 (39 active tbc)	64.5%:contaminated 89.7%: Active tbc	-	-	-
Öznur Ak,2009 Jpn J Infect Dis	Pulm, extra pulm tbc	Turkey	65	75% (pulm tbc), 76.2% (extra pulm tbc)	-	6-40%	9-60%
Nobuyuki Harada 2008 Journal of Infection	Tbc	Japan	100 Tbc (culture and/ or PCR(+)), 168 healthy	QFT-GIT: 92.6% QFT-G:81.4%	QFT-GIT/G: 98.8%	-	-
Kelly Aparecida, 2008, Clinical and Vaccine Immunology	Pulmonary Tbc (22 culture(+))	Brazil	29	86%	100%	-	-
V Bartu, 2008 The Journal of International Medical Research	Tbc	Prague	53	86%	-	8%	26%
Ilaria Sauzullo, 2008 Diagnostic Microbiology and Infectious Disease	Suspected with Tbc	Italy	369 (Active tbc 96, latent tbc 42)	73% (active tbc)	89% (active tbc)	-	-
Soysal 2008 Int J Tuberc Lung Dis	Active pulm tbc	Turkey	100 tbc, 47 healthy	78%	89.4%	-	-
Kazue Higuchi 2008 Med Microbiol Immunol	Tbc (46 Pulm, 1 Milier)	Japan	47 tbc, 84 healthy	87.2%	98.8%	-	-

gamma releasing assay) in the diagnosis of intestinal tuberculosis, the use of PPD and IGRA in the diagnosis of tuberculosis were reviewed first. IGRA tests depend on the principle that individuals, whose T cells are sensitized with tuberculosis antigens, generate IFN-gamma when they come across mycobacterial antigens. The two proteins of mycobacterium tuberculosis, ESAT-6 and CFP-10, are addressed. Quantiferon Tb-Gold and Elispot are the two tests in common commercial use. Quantiferon Tb-Gold is widely used in Turkey.

Numerous studies demonstrated that IGRA is more sensitive and specific compared with PPD in immunocompetent patients. However, further studies are required (22).

BCG vaccination may result in false PPD positivity. Receiving corticosteroid therapy in the last 1 month or MTX therapy in the last 3 months may result in false PPD negativity. Booster PPD (in 1 to 8 months) is recommended in patients who are PPD (-) and will receive immunomodulatory treatment. Booster PPD helps to diagnose latent tbc up to the rate of 8% to 14% in patients with an inflammatory bowel disease or a rheumatologic disease. False PPD negativity may be obtained in patients with active IBD who are not receiving immunosuppressive treatment. PPD>5 mm should accepted as positive in the diagnosis of latent tbc (22). Meta analyses published in 2007 report PPD sensitivity as %71 and specifity as 97%, and IGRA sensitivity as 76% and specifity as 97%. The rate of PPD (-)/IGRA (-) was %49.3 and PPD (-)/IGRA (+) was 5.1% (23).

In a study from Greece, PPD and IGRA sensitivities were reported as 74% and 85.1%, respectively, in the diagnosis of active tbc. In a study from Turkey, the PPD sensitivities were 68.2% in pulmonary tbc and 62% in extra pulmonary tbc, and the IGRA sensitivities were 75% in pulmonary tbc and 76.2% in extra pulmonary tbc (24, 25). In another study carried out in Japan, 172 infected patients (39 active tbc) were studied. The IGRA sensitivity was found to be 89.7% in the diagnosis of active tbc (26). Nobuyuki Harada et al reported the IGRA sensitivity and specifity as high as 92.6% and 98.8 respectively (27).

b. Intestinal Tbc (PPD-IGRA)

Because of the limited data, the importance of

PPD and IGRA tests are unknown in the diagnosis of intestinal tbc, and urgent studies are required. In a series of 11 patients with intestinal tuberculosis, PPD sensitivity was determined as 63.9%. In another series including 29 patients with intestinal tuberculosis, it was reported as 86% (2, 6). IGRA test was evaluated in two patients with intestinal tbc and found to be positive in both of them in a case report (28).

The results of the sensitivity and specifity of the diagnostic methods are shown in the tables (Table 3-7).

CONCLUSION

PPD test, at least 8 biopsies, tissue ARB, tissue PCR and tissue culture are recommended in the diagnosis of intestinal tbc.

There are not sufficient data regarding the importance of IGRA test in the diagnosis of intestinal tuberculosis. Quantiferon test, is more sensitive in cases with active tuberculosis compared with the PPD test and is not affected by the BCG vaccination. However, this increase in the sensitivity is about 5% and the cost of the IGRA test is prominently higher than PPD test. Therefore, the replacement of the IGRA test with the PPD for routine screening of tbc is not likely under the circumstances of our country. Nevertheless, the IGRA test may be used in selected cases. Based on these findings, national recommendations for the diagnosis of intestinal tuberculosis are seen in the box.

Recommendation:

For the diagnosis of intestinal tuberculosis, at least 8 biopsies should be performed during the colonoscopy for histopathologic evaluation. ***(EL 4 RG C)***

Tissue ARB and tissue culture are required for the diagnosis of intestinal tbc and the positivity of any of them is prognostic; however their negativity does not exclude intestinal tbc diagnosis. ***(EL 4 RG C)***

Tissue PCR evaluation is recommended and its positivity is significant. (Could be tested in old specimens retrospectively which is an advantage.) A negative result does not exclude the diagnosis of tbc. ***(EL 4 RG C)***

PPD test should be performed as a complementary test. ***(EL 4 RG C)***

The use of the IGRA test is recommended for the diagnosis of intestinal tbc in selective cases. ***(EL 4 RG C)***

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