FULL PAPER

Role of Tc-99m Ethambutol Scintigraphy in Diagnosing Tuberculosis in children with Scoring Systems as Diagnostic Approach

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Abstract

Background. Tuberculosis (TB) is world's endemic infection, especially in developing countries. In children, tuberculosis infection can be seen as the great masquerade because have non-specific symptoms. Diagnosis of tuberculosis infection is more difficult in children because of chest x-ray are less specific; standard sputum samples are often difficult to collect; lower bacterial loads made microscopic and culture more difficult. Bacteriological examination as a gold standard is limited used in children. Several diagnostic approaches are developed to overcome diagnosis problem of TB in children. Various scoring systems and diagnostic classifications have been developed as screening test that may help clinical judgment in diagnosing tuberculosis in children. Among different scoring systems, the Keith-Edwards scale (WHO TB scores) is the most widely used in clinical setting. Kenneth-Jones' criteria (KJS) has been used in several centers as diagnostic approach in diagnosing TB. ^{99m}Tc-Ethambutol SPECT/CT can be used to detect and to localize tuberculosis infection. The aim of this study is to describe the role of ^{99m}Tc-Ethambutol Scintigraphy in diagnosing tuberculosis in children based on KJS and WHO TB score as diagnostic approaches.

Material and methods. Our study population comprised of 84patients (42 boys and 42 girls with age range 3–168 months). SPECT/CT was done 1 and 3 hours after injection of 7-444 MBq ^{99m}Tc-Ethambutol. Sedation was given before acquisition for uncooperative patients to avoid movement. KJS and WHO TB score were used as diagnostic approach in

diagnosing TB. KJS consists of variables such as: AFB smear, chest X-ray, BCG vaccination, granulomatous lesions in histophatological result, physical findings, tuberculin test, history of contact with TB patient or sputum smear positive, age below 2 years, history of anti tuberculosis drugs, and degree of malnutrition. According to KJS scoring system, score ≥ 7 indicates unquestionable TB. The variables in WHO TB score includes : duration of illness, nutritional state, history TB in family, tuberculin test, malnutrition, symtomp of fever and night sweats, local clinical findings of tuberculosis lesions. WHO TB scores ≥ 7 indicates a high likelihood of TB.

Result. From total 84 patients, positive ^{99m}Tc-Ethambutol scintigraphy were found in 52 of 58 patients with KJS ≥ 7 (89.66%) and 53 of 58 patient with WHO TB score ≥ 7(93.10%). Negative ^{99m}Tc-Ethambutol scintigraphy was found in 32 subjects with KJS criteria < 7 (38.1%), and 30 subjects with WHO TB score < 7 (35.7%). Discordance of these results: 7 subjects (positive scintigraphy while negative KJS criteria), 6 subjects (positive scintigraphy while negative WHO TB score), and 1 subject (negative scintigraphy while positive KJS criteria or WHO TB score). Agreement result between ^{99m}Tc-Ethambutol and KJS criteria; kappa index 0.843 ($p < 0.001$). Agreement result between ^{99m}Tc-Ethambutol with WHO TB score; kappa index 0.815 ($p < 0.001$). There was no adverse effect observed from all subjects. ^{99m}Tc-Ethambutol is safe, effective, and non-invasive diagnostic modality that can be used in children.

Conclusion. ^{99m}Tc-Ethambutol can be used as one of diagnostic modality to diagnose TB in children.

Key words: Tuberculosis, children, Kenneth-Jones' criteria, WHO TB sore, ^{99m}Tc-Ethambutol

Background

Tuberculosis (TB) is a global endemic infection problem, particularly in developing countries. Approximately one third of the world population was infected with latent tuberculosis, and each year there were about 1.6 million people in the world die from tuberculosis.[1] eleven percentage of all new worldwide cases of tuberculosis were found in children.[2]It has been estimated, that the burden of childhood tuberculosis in some endemic areas were as high as 40%.[3]

TB can involve any part of the body as a single or multiple sites. Multifocal tuberculosis is characterized by the presence of multifocal tuberculosis areas in the same or different organs. Extrapulmonary tuberculosis usually presents with diagnostic problem than pulmonary tuberculosis. Difficulty on diagnosis of tuberculosis may lead to a delay in treatment of tuberculosis infection. In addition, extrapulmonary tuberculosis involves relatively in accessible sites for bacteriologic confirmation.In children, tuberculosis infection can be seen as the great masquerade because have non-specific symptoms. Diagnosis of tuberculosis infection is more difficult in children. The initial investigation of tuberculosis patient is chest x-ray, but this modality is less helpful in children because the findings can overlap with other respiratory pathology.[4]

Sputum samples are often difficult to collect and not helpful for culture due to the low bacterial load and children often swallow their sputum. Lower bacterial loads made microscopic and bacterial culture more difficult. Bacteriological examination to visualize bacteria as a gold standard is limited used in children.[5] Bacteria are only visible in 10-15% of cases of childhood tuberculosis compared with 60% in adults by using Ziehl-Neelson staining or fluorescence microscopy.[6]

Several diagnostic approaches are developed to overcome diagnosis problem of TB in children. Various scoring systems and diagnostic classifications have been developed as screening test that may help clinical judgment in diagnosing tuberculosis in children. Among different scoring systems, the Keith-Edwards scale (WHO TB score) is the most widely used in clinical setting. Modified Kenneth-Jones' criteria (MKJ) had been used in several centers as diagnostic approach in diagnosing TB.[7,8] ^{99m}Tc-Ethambutol SPECT/CT is one of imaging modality in nuclear medicine can be used to detect and localize tuberculosis infection. The aim of this study was to evaluate the role of ^{99m}Tc-Ethambutol Scintigraphy in diagnosing tuberculosis in children based on KJS criteria and WHO TB scores as diagnostic approaches.

Material and methods

Retrospective cross sectional study was conducted in Department of Nuclear Medicine Dr. Hasan Sadikin General Hospital involving subjects with inclusion criteria suspected of having tuberculosis infection and never been diagnosed and treated as tuberculosis. ^{99m}Tc-Ethambutol SPECT/CT scintigraphy was done in 1 and 3 hours after intravenous injection of 67-444 MBq ^{99m}Tc-Ethambutol. Sedation was given prior to data acquisition for uncooperative patient to avoid movement. Positive ^{99m}Tc-Ethambutol scintigraphy was considered as tuberculosis infection if specific increased pathological uptake was found. KJS criteria and WHO TB scores were used as diagnostic approaches in diagnosing TB.

KJS criteria consists of variables such as: AFB smear, chest X-ray, BCG vaccination, granulomatous lesions in histophatological result, physical findings, tuberculin test, history of contact with TB patient or sputum smear positive, age below 2 years, history of anti tuberculosis drugs, and degree of malnutrition. According to KJS scoring system, score 7

or more indicate unquestionable TB; 5-6 points indicate probable TB, therapy may be justified; 3-4 points indicate that further investigations are needed.[7,8]

The variables in WHO TB score include: duration of illness, nutritional state, history TB in family, tuberculin test, malnutrition, symptom of fever and night sweats, local clinical findings of tuberculosis lesions.WHO TB score $\geq$ 7 indicates a high likelihood of TB. Statistical analysis using Kappa statistic (Kappa coefficient of agreement=k) was used to analyze the agreement between as ^{99m}Tc-Ethambutol scintigraphy and KJS criteria, and between as ^{99m}Tc-Ethambutol scintigraphy and WHO TB scores.

Results

This study was involving 84 subjects who met the inclusion criteria, consist of 42 boys and 42 girls with age range 3-168 months old. Positive and negative result of ^{99m}Tc-Ethambutol scintigraphy, KJS criteria, and WHO TB score were 58 (69,0%) and 26 (31,0%), 52 (61,9%) dan 32 (38,1%), 53 (63,1%) dan 31 (36,9%) respectively (Table 3). Concordance result between ^{99m}Tc-Ethambutol scintigraphy and KJS criteria was found in 76 (90%) subjects and discordance in 8 (10%) subjects. Positive concordance was found in 51 subjects and negative in 25 subjects. Discordance between positive ^{99m}Tc-Ethambutol scintigraphy and negative KJS criteria was found in 7 subjects and on the opposite negative ^{99m}Tc-Ethambutol scintigraphy and positive KJS criteria was found in one subject. Agreement analysis between results of ^{99m}Tc-Ethambutol scintigraphy and KJS criteria was done and kappa index was kappa index 0.843 with p value< 0.001 (Table 4).

Concordance result between ^{99m}Tc-Ethambutol scintigraphy and WHO TB score was found in 77 (92%) subjects and discordance in 7 (8%) subjects. Positive concordance was found in 52 subjects and negative in 25 subjects. Discordance between positive ^{99m}Tc-

Ethambutol scintigraphy and negative WHO TB score was found in 6 subjects and on the opposite negative ^{99m}Tc-Ethambutol scintigraphy and positive WHO TB score found in one subject. Agreement analysis between results of ^{99m}Tc-Ethambutol scintigraphy and WHO TB score was done and kappa index 0.815 with p value < 0.001) (Table 5).

There were no adverse effects observed from all subjects underwent ^{99m}Tc-Ethambutol scintigraphy.

Table 3. Result of ^{99m}Tc-Ethambutol scintigraphy, MKJ criteria, and WHO TB score.

Variable	(n=84)
• ^{99m}Tc-Ethambutolscintigraphy	
Positive	58 (69,0%)
Negative	26 (31,0%)
• Moddified Kenneth Jones criteria	
Positive	52 (61,9%)
Negative	32 (38,1%)
• WHO TB score	
Positive	53 (63,1%)
Negative	31 (36,9%)

Table 4. Agreement result between ^{99m}Tc-Ethambutol scintigraphy, KJS criteria

		KJS criteria		p value	Kappa coefficient
Ethambutol scintigraphy	Positive (n=52)	Negative (n=32)	Total	<0.001	0,843
Positive	51 (98,1%)	7(21,9%)	58		
Negative	1 (1,9 %)	25(78,1%)	26		

Table 5. Agreement result between ^{99m}Tc-Ethambutol scintigraphy and WHO TB score.

	WHO TB score		Total	p value	Kappa coefficient
	Positive (n=53)	Negative (n=31)			
Ethambutol scintigraphy				<0.001	0,815
Positive	52 (98,1%)	6 (19,4%)	58		
Negative	1 (1.9 %)	25 (80,6%)	26		

Table 6. Comparison of all diagnostic modality.

	Diagnosis of TB		Total	p value
	Positive	Negative		
KJS criteria	52 (61.9%)	32 (38.1%)	84	0,583
WHO TB score	53 (63,1%)	31 (36.9%)	84	
Ethambutol scintigraphy	58 (69,0 %)	26 (31,0%)	84	

Discussion

Tuberculosis (TB) is one of the most important causes of seriously infectious due to Mycobacterium tuberculosis. TB is more likely to develop severe disease in infant and children.Children are exposed to TB usually through contact with infectious adults and as long as those adults remain untreated they will continue to be at risk for TB. The diagnosis of TB in children is notoriously difficult as the early symptoms and signs are easily missed and it is hard to confirm by mycobacterial culture even with sufficient laboratory facilities. It is important to get appropriate specimen but in some location its need an invasive procedure to obtain it. Positive microbilogical test for TB was found only 10-15% in children with TB. In developing countries sometime the empirical treatment with anti tuberculosis drug usually was use to diagnose TB.[8-14] This difficulty resulting misdiagnosis of TB in some children or may be falsely negative TB. Thus, other diagnostic modality which is safe, non-invasive, and effective to diagnose tuberculous infection in children is needed.

There are scoring systems proposed by Stegen*et al*,Nair and Philip, etc. Scoring system proposed by Dr. Keith Edwards (Table 1)] was endorsed and advocated by WHO for use in National TB Control Programs of different countries. The clinical criteria were relevant as predictors of TB in children are as follow; contact history with a case of TB, positive PPD skin test, persistent cough, under weight, and unexplained/prolonged fever.[8] Cough has not been taken as criteria in Keith Edwards's scoring system. In this study we

found 52 (61.9%) of subjects showed positive TB by using Modified Keith Edwards scoring system7 or more dan 32 (38.1%) were negative with score less than 7. Sarkar et al found the sensitivity, specificity, and positive prediction value of the KJS scoring system were 84.9, 78, and 80.36%, respectively. Pondicherry showed the sensitivity and specificity of KJS scoring system was 91% and 88%, respectively.[8] By using WHO TB score we found positive TB with score 7 or more in 53 (63,1%) subjects and negatif in 31 (36,9%) subjects.

Ethambutol is dextro-2,2.-(ethylenediimino)-di-1-butanol) was initially reported to have anti-tuberculosis activity in 1961. Ethambutol is bacteriostatic agent used as treatment for tuberculosis infection. The primary pathway affected by ethambutol appears to be that of arabinogalactan biosynthesis through inhibition of cell wall arabinan polymerization.[15] Ethambutol could be labeled by ^{99m}Tc labeled. This radiopharmaceutical agent can be used as diagnosing modality to detect and localize tuberculosis infection. The highest binding capacity (84,3%) between this radiopharmaceutical and micobacterium tuberculosis was found at 1 hour after contact. The binding capacity decreased to 63.4% and 23.2% at 2 and 24 hours respectively. The optimal images are taken at 1 and 2 hours post injection of ^{99m}Tc-etambutol.[16,17]

^{99m}Tc-ethambutol scan is specific to localize Micobacterium sp. and more sensitive in deep seated infection. SPECT-CT with ^{99m}Tc-Ethambutol is non-invasive diagnostic modality enable whole body scan can be used to detect multiple lesion of pulmonary and extra-pulmonary tuberculosis infection. In this study positive and negative result of ^{99m}Tc-Ethambutol scintigraphy were found in 58 (69%) subjects and 26 (31%) subjects respectively. Concordance result between ^{99m}Tc-Ethambutol scintigraphy and KJS criteria was found in 76 (90%) subjects and discordance in 8 (10%) subjects. Positive concordance was found in 51 subjects and negative in 25 subjects. Discordance between positive ^{99m}Tc-

Ethambutol scintigraphy and negative KJS criteria was found in 7 subjects and on the opposite negative ^{99m}Tc-Ethambutol scintigraphy and positive KJS criteria was found in one subject. Kappa coefficient Agreement analysis between results of ^{99m}Tc-Ethambutol scintigraphy and KJS criteria was done and kappa index was 0.843 with p value < 0.001 (Table 4). Its mean that the result of ^{99m}Tc-Ethambutol scintigraphy was almost perfect agreement with result of KJS criteria in diagnosis of TB in children.

Concordance result between ^{99m}Tc-Ethambutol scintigraphy and WHO TB score was found in 77 (92%) subjects and discordance in 7 (8%) subjects. Positive concordance was found in 52 subjects and negative in 25 subjects. Discordance between positive ^{99m}Tc-Ethambutol scintigraphy and negative WHO TB score was found in 6 subjects and on the opposite negative ^{99m}Tc-Ethambutol scintigraphy and positive WHO TB score found in one subject. Kappa coefficient Agreement analysis between results of ^{99m}Tc-Ethambutol scintigraphy and WHO TB scores was done and kappa index was 0.815 with p value < 0.001) (Table 5). Its mean that the result of ^{99m}Tc-Ethambutol scintigraphy was almost perfect agreement with result of WHO TB scores in diagnosis of TB in children.

The advantage of SPECT-CT ^{99m}Tc-Ethambutol is the capability to provide more accurate anatomical site of infection. While high scoring systems as screening test may be considered as wide tuberculosis infection or multifocal tuberculosis.

Conclusion

^{99m}Tc-Ethambutol is promising imaging diagnostic modality to detect and localize the site of tuberculous infection in children. This modality is safe, effective, and non-invasive diagnostic modality that can be used in children.

Referrences

1. World health organisation 2005; fact sheet number 104
2. Donald PR. Childhood tuberculosis: out of control? CurrOpinPulm Med 2002;8:178-82.
3. Nelson L, Wells CD. Global epidemiology of childhood tuberculosis. Int J Tuberc Lung Dis 2004;8:636-47.
4. Donald PR. Childhood tuberculosis: out of control? CurrOpinPulm Med 2002;8:178-82.
5. Zar HJ, Hanslo D, Apolles P, Swingler G, Hussey G. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. Lancet 2005;365:130-4.
6. Shingadia D, Novelli V. Diagnosis and treatment of tuberculosis in children. Lancet Infect Dis 2003;3:624-32
7. WHO. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2006.
8. Sarkar S, Paul DK, Chakrabarti S, Mandal NK, and GhoshalAG. The Keith Edward scoring system: A case control study. Lung India. 2009 Apr-Jun; 26(2): 35–37.
9. Sharma MP, Bhatia V. Abdominal tuberculosis. Indian J Med Res. 2004;120:305-15.
10. Khuroo MS, Khuroo NS. Abdominal tuberculosis. Dalam: Madkour MM, Saif AA, Shahed MA, Moutaery KR, Kudwah AA, penyunting. Tuberkulosis. Berlin: Springer-Verlag; 2004. h. 659-75.
11. Cruz AT, Starke JR. Pediatric tuberculosis. Pediatr. Rev.2010;31:13-26.

12. Heda M Nataprawira, Komalia H. Abdominal tuberculosis in children. Paediatr Indones. 2001:41:155-59.
13. Mandalakas A, Starke J. tuberculosis and nontuberculosis mycobacterial disease. Dalam: ChernickV, Boat TF, Wilmott RW, Bush A, penyunting. Kendig's disorders of the respiratory tract in children.Edisi ke-7. Philadephia: Saunders; 2006. h. 507-29.
14. Basu S, Ganguly S, Chandra PK, Basu S. Clinical profile and outcome of abdominal tuberculocis in Indian children. Singapore Med J. 2007;48(10):900-5.
15. Mikusova, K., R. A. Slayden, et al. (1995). "Biogenesis of the mycobacterial cell wall and the site of action of ethambutol." Antimicrob Agents Chemother 39(11): 2484-2489.
16. Kartamihardja AH, Oekar NK, Juwita R. Pencitraan dengan radionuklid 99mTc-Etambutol untuk diagnosis tuberkulosis ekstrapulmonal (penelitian pada hewan percobaan). MKB. 2006;38(3):116-21.
17. Singh N, Bhatnagar A. Clinical evaluation of efficacy of 99mTc-ethambutol in tubercular lesion imaging. Tuberc. research and treat. 2010: 1-9.