Original Research Article

Clinico-radiological criteria versus GeneXpert for diagnosis of pediatric tuberculosis

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ABSTRACT

Background: Diagnosing tuberculosis in children remains a challenge especially in low-income countries. The aim of this study was to assess the performance of the scoring system combined to chest x-ray images compared to GeneXpert for diagnosis of pediatric tuberculosis.
Methods: A retrospective diagnostic accuracy study was carried out on hospitalized children aged 0 to 14 years old, tuberculosis suspect in the pediatric department of the Tsaralalana mother child university hospital center from August 2018 to June 2020.
Results: Fifty-one medical files were retained. The mean age was 4 ± 2 years old with a sex ratio of 1.55. The reason for consultation was dominated by respiratory signs (56.9%). The GeneXpert was positive in 58.9% of cases. The chest X-ray images were pathological in all cases, dominated by images of condensation or infiltration (72.5%). WHO score was positive (≥7) in 72.5% of cases. The clinico-radiological criteria had a sensitivity of 13.3-63.3%, a specificity of 61.9-95.2%, positive predictive values of 1.5-6.9% and negative predictive values of 98.8-99.3%.
Conclusion: Clinico-radiological criteria could be useful in individual diagnosis of pediatric tuberculosis.

Keywords: Pediatric tuberculosis, Sensitivity and specificity, Scoring system, Thoracic radiography

INTRODUCTION

Tuberculosis (TB) is a contagious infectious disease caused by Koch's bacillus or *Mycobacterium tuberculosis*. Its localization is essentially pulmonary but can also be extra-pulmonary. It is a major public health problem, especially in developing countries. According to the report of the world health organization (WHO), 1.1 million children have had TB and 230.000 have died.[1] In Sub-Saharan Africa, 15 to 20% of TB cases are pediatric cases.[2] TB in children is a major cause of mortality due to the rapid development of severe forms.[1]

Madagascar is one of endemic areas of TB. The estimated prevalence of TB was 413 cases per 100000 people with a mortality rate of 52 per 100.000 people. The estimated incidence of TB was 236 cases per 100.000 people.[1,3]

The diagnosis of this infection remains difficult in children because the clinical and radiological signs are often not specific. Also, obtaining sputum is difficult; the sample obtained may contain a low bacillary load, limiting the reliability of direct microscopy. The gold standard for diagnosis is the isolation of *Mycobacterium tuberculosis* by culture or molecular methods. However, these references standard exams have some limitations. Culture is long, not commonly practiced and could detect less than 40-50% of cases of TB in children.[4-6] Molecular tests are expensive and high technology, thus limiting its accessibility in developing countries like Madagascar.[6] In

current practice, in the absence of bacteriological evidence, the main arguments for TB diagnosis are clinical, radiological associated with notion of contact with TB patient. Until now, scoring system based on clinical items with controversial reliability, is used in Madagascar.[3,7] Scoring system is good tool for public health purpose but it might be less effective for individual diagnosis because of these elements of clinical presumption are not very specific.[8,9] In addition, some elements of the score are not assessable or unreliable in the early stage of disease. These clinical criteria combined to radiological criteria could help low-income countries to do individual diagnosis of childhood TB if they prove to be efficient. Thus, this preliminary study was conducted to assess the validity of clinico-radiological criteria in the diagnosis of TB in children in the Malagasy context. Its main objective is to assess the intrinsic and extrinsic performances of the scoring system coupled to chest X-ray (CXR) for the diagnosis of pediatric TB compared to molecular method, GeneXpert.

METHODS

This was a retrospective diagnostic accuracy study covering period between August 2018 and June 2020. The study conducted at mother-child university hospital Tsaralalana which is only pediatric hospital with GeneXpert device. This pediatric reference hospital, located in city center, receive children aged from 0-14 years old. Hospital has avg. of 3.500 annual admissions.

The study included all hospitalized children TB suspect, aged from 0 to 14 years and having received GeneXpert and having a good quality CXR. Exclusion criteria was incomplete medical records. The sampling was exhaustive. The sample size was 51 children.

All data were collected on medical records. The variables studied were socio-demographic variables, Bacillus Calmette-Guerin (BCG) vaccination status, clinical variables (anthropometric parameters, reasons for admission, clinical signs, score for TB diagnosis), paraclinical data (Tuberculin skin test results, human immunodeficiency virus test results, CXR images, GeneXpert results) and localization of TB infection.

The index tests were WHO's proposed score for TB diagnosis (modified Keith Edwards) and CXR pathological images. The WHO score is based on 11 criteria, each rated from 0 to 4 (Table 1).[3] Score was positive if the overall rating is greater than or equal to 7.[3,10] Interpretation of the radiological images was carried out by a paediatrician then validated by a radiologist. All CXR pathological images of TB infection were considered. GeneXpert, a molecular method, is a cartridge-based real-time polymerase chain reaction (PCR).[11] GeneXpert was chosen as reference standard in this study because the results are superior to smear microscopy and comparable to culture with shorter turn-

around time.[12,13] Also, WHO recommends GeneXpert for diagnosis of TB in children.[14]

Combination of clinico-radiological criteria were compared to GeneXpert. The diagnostic accuracy of clinico-radiological criteria was presented in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence intervals (95% CI). Chi square and exact Fisher tests were used for the comparison of proportions. A two-sided $p<0.05$ was considered statistically significant. All statistical analyzes were performed using Epiinfo7® v7.1.5.2 software.

Given the retrospective design of this study, only medical records were reviewed. There was no direct interaction between the investigator and people whose medical records targeted by the study. This study respected the ethical principles of the declaration of Helsinki. The study obtained authorization of the Management of the hospital. Patient anonymity was respected during data collection and analysis.

RESULTS

Of the 5091 medical records of hospitalized children during study period, 65 files of children TB suspect were selected. Only 51 children were included in the study. Thirteen patients were not included in the study because either they did not benefit from GeneXpert, or their CXR was of poor quality. One patient with incomplete medical record was excluded from the study. Flow diagram of participants is shown in Figure 1.
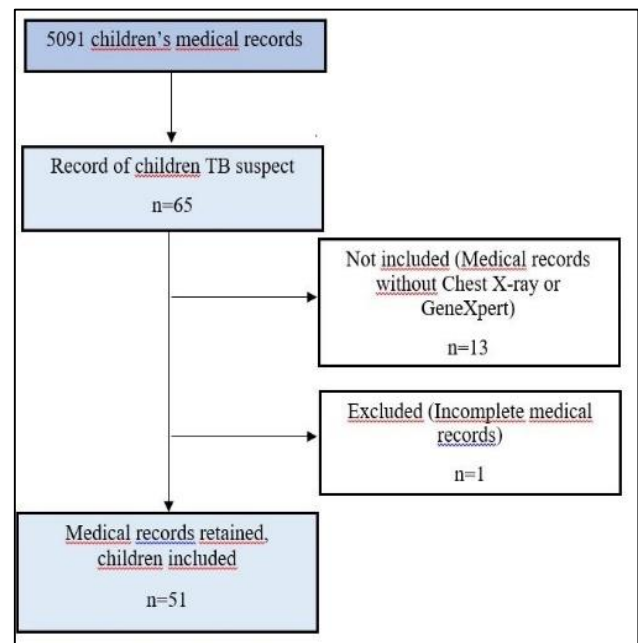
Figure 1: Flow diagram of participants.

Hospital frequency of TB suspect was 1.3%. The mean age of children was 4±2 years with extremes of 2 months

and 14 years. Children under 5 years of age were most affected (66.7%). A male predominance was found (sex ratio of 1.55). Low socioeconomic status was found in 52.9% of cases. The sociodemographic characteristics of hospitalized children TB suspect are presented in Table 2.

More than three-quarters of patients (78.4%) were vaccinated by the BCG. The main reasons for admission of children were dominated by respiratory signs: dyspnea (35.5%), chronic cough (21.6%). Clinically, among the general signs were anorexia (78.4%), fever (74.5%) and weight loss (72.6%). The clinical presentation was dominated by respiratory signs. The most reported signs were cough (96.1%) followed by dyspnea (86.3%), chest pain (15.7%) and hemoptysis (2%). Acute malnutrition was observed in 72.5% of cases. Frequency of acute malnutrition was 85.7% in children with a negative GeneXpert and 63.3% in children with confirmed TB. About clinical scoring system, 37 children (72.5%) had a positive score (≥7). Regarding topography of TB infection, pulmonary form was the most common (74.5%) of which 54.9% was biologically proven. Isolated extrapulmonary TB was found in 25.5% of cases. The mixed form (pulmonary TB associated with extra-pulmonary TB) was found in 29.4% of cases.

Tuberculin skin test (TST) was only performed in 27 patients, 2 of whom had a positive TST. No Human Immunodeficiency Virus (HIV) co-infection was found in the 45 children who benefit from serology. GeneXpert test for TB was positive in 58.9% of cases, of which 54.9% were carried out on sputum and 4% on cerebrospinal fluid. On CXR, the main radiological abnormalities found were: condensation or infiltrate (72.5%); pulmonary cavity (35.3%), pleural effusion (27.5%), miliary (21.6%), hilar adenopathy (15.7%) and atelectasis (9.8%).

Index test and reference standard were generally performed on same day or with a time interval of few days. No adverse events were reported in medical records from performing index test or reference standard. The diagnostic accuracy of clinico-radiological criteria compared to GeneXpert was assessed. The association of at least 2 pathological CXR images with a positive WHO score was significantly associated to positive GeneXpert ($p=0.005$). Positive WHO score associated with infiltrate or condensation on CXR had the highest sensitivity being 63.3% (95% CI 43.9-80.1) but the lower specificity 61.9% (95% CI 38.4-81.9). The association of positive WHO score and miliary or atelectasis had the highest specificity, both being 85.7% (95% CI 63.7-96.9). The PPV of clinico-radiological criteria ranged from 1.5% to 6.9%. The NPV of clinico-radiological criteria ranged from 98.7% to 99.3%. The association of positive WHO score and condensation/infiltrate or miliary or association of radiographic images had the highest NPVs being all 99% (Table 3).

Table 1: WHO scoring system adopted in this study.

Features		Points		
		1	**2**	**3**
Duration of cough/other symptoms of illness		2-4 weeks		>4 weeks
Nutritional status (Weight for height)		< -2SD		<-3SD
Malnutrition not improving after period of		2-4 weeks		>4 weeks
Family history of TB (contact with a TB patient)		Former TB patient		Person with positive smear actually or under treatment
TST results	With scar vaccine	Induration of 15-20 mm	Induration ≥20 mm	
	Without scare vaccine	Induration of 10-15 mm	Induration ≥15 mm or phlyctenular	
Other features				**Points if present**
Unexplained fever with no response to antimalarial drugs and/or two antibiotics				2
Adenopathies				3
Joint or bone swelling				2
Abdominal mass or ascites				3
Neurological signs and/or lymphocytar formula				3
Angle deformity of spine				4

SD: Standard deviation; TST: Tuberculin skin test; TB: Tuberculosis.

Table 2: Sociodemographic characteristics of hospitalized children TB suspect.

Variables	N	Percent (%)
Children's age (Years)		
<5	34	66.7
5-10	9	17.6
>10	8	15.7

Continued.

Variables	N	Percent (%)
Place of residence		
Urban	33	65
Rural	18	35
Socioeconomic status		
Low	27	52.9
Medium	12	23.5
High	1	2
Not defined	11	21.6

Table 3: Bivariate analysis of performance of association WHO score-pathological chest X ray images compared to GeneXpert in the diagnosis of tuberculosis.

Variables	Reference standard		Se (%)	Sp (%)	PPV (%)	NPV (%)	P
	GE +, n=30	GE-, n=21					
Condensation/ infiltrate + score ≥7	19	8	63.3 (43.9-80.1)	61.9 (38.4-81.9)	2.1 (1.2-3.9)	99 (98.6-99.6)	0.09
Miliary + score ≥7	8	1	26.7 (12.3-45.9)	95.2 (76.2-99.9)	6.9 (1-35.3)	99 (98.7-99.2)	0.06
Hilar adenopathy + score ≥7	9	2	30 (14.7-49.4)	90.5 (69.6-98.8)	4 (1-14.7)	99 (98.7-99.2)	0.1
Atelectasis + score ≥7	4	1	13.3 (3.8-30.7)	95.2 (76.2-99.9)	3.6 (0.4-23.5)	98.8 (98.6-99)	0.39
Pleural effusion + score ≥7	5	3	16.7 (5.6-34.7)	85.7 (63.7-96.9)	1.5 (0.4-5.4)	98.7 (98.4-99)	1
Cavity + score ≥7	10	3	33.3 (17.3-52.8)	85.7 (63.7-96.9)	3 (0.9-9)	98.9 (98.6-99.2)	0.19
Associated images[a] + score ≥7	18	4	60 (40.6-77.3	80.9 (58.1-94.5)	4 (1.6-9.5)	99.3 (98.9-99.6)	0.005

[a]The associated images were: condensation/infiltrate-pulmonary cavity (n=7), condensation/infiltrate-hilar adenopathy (n=7), condensation/infiltrate-pleural effusion (n=4), miliary-pleural effusion (n=3), miliary-hilar adenopathy (n=1). Se=Sensibility; Sp=Specificity; PPV=Positive predictive value; NPV=Negative predictive value.

DISCUSSION

In this study, children below 5 years were the most affected by TB. This finding is supported by other published studies.[9,15,16] This predominance could be explained by the vulnerability of the immune system of children under 5 years of age.

The majority of patients (78.4%) were vaccinated with BCG as found in other studies.[16,17] These results prove that BCG vaccine does not protect against all forms of TB but has the main purpose of protecting young children from serious forms of TB such as TB meningitis, miliary TB. Our results are similar to those of other studies finding respiratory signs as the predominant clinical signs.[18,19]

The positivity rate of the TST was low (7.4%) compared to that found by Soumana et al (85.7%).[20] This low positivity rate in our series could be linked to several false negatives related to a technical error or an alteration of cellular immunity by malnutrition, HIV infection, hematogenous TB.[21] A positive TST is one of the important diagnostic criteria for TB in a sick child.

However, a negative TST does not eliminate diagnosis of TB.[21] Also, TST could not be performed in all participants in this study related to absence of reagent.

On CXR, the most common radiological abnormality was infiltrate or condensation (72.5%). This finding agrees with data from literature on the high frequency of parenchymal abnormalities in pediatric TB.[22,23] Furthermore, mediastinal or hilar adenopathies, although infrequent (15.7%), represents the characteristic lesion of TB in children.[22,24]

The scoring criteria used in the study were oriented towards a completely clinical diagnostic approach and therefore excluded laboratory data except for TST and lymphocyte formula on cerebrospinal fluid examination. However, scoring system based on clinical items has controversial reliability.[7] Some studies have reported good performances with a sensitivity varying between 76.9 and 91% and specificity between 88 and 90%, while others have found poor performances with a sensitivity of 85% and a specificity of 25%.[25-27] In addition, the interpretation of the scoring system is biased in early stage of disease regarding duration of cough, nutritional

status, lack of improvement in nutritional status, unexplained fever with no response to antimalarial drugs and/or two antibiotics. Considering the items of this score, the score could be higher in those with extra-pulmonary TB than pulmonary TB. Otherwise, with regard to nutritional status, it turned out to be an important factor in determining the diagnostic score. Nevertheless, in this study, more than two-thirds (85.7%) of children with a negative GeneXpert had acute malnutrition. This raises the question of the relevance of this indicator in a context of high prevalence of malnutrition like in Madagascar. Some authors said that the scoring system is a better tool for mass screening in public health than for individual diagnosis of TB.[8,9]

Given that the scoring system used in our study did not take into account TB pleural/pericardial effusion, CXR is a complementary tool for the diagnosis of intrathoracic tuberculosis. Moreover, Palmer et *al.* found that enlargement of perihilar and/or paratracheal lymph nodes, bronchial deviation/compression, cavities, expansile pneumonia and pleural effusion had a specificity of more than 90% for confirmed TB.[28]

In our study, clinico-radiological criteria had good specificity (>80%) except of positive WHO score associated with infiltrate/condensation (61.9%). A positive WHO score associated with miliary, hilar adenopathy, and atelectasis had a specificity of more than 90% for confirmed TB by GeneXpert. According to literature, specificity is essential for any diagnostic test, but no diagnostic test is rigorously specific and has perfect sensitivity.[29,30] Thus, for individual diagnosis, it is recommended to use very specific tests; while for mass screening, it is preferable to use very sensitive tests even if they give false positives.[29,30] Therefore, these clinico-radiological criteria could be used to establish individual diagnosis of TB in children, especially in a developing country like ours where CXR is more accessible than the reference methods.

However, this study had some limitations. TST could not be performed in all participants, which could constitute a bias in interpreting of WHO score. Diagnostic practices were also assessed retrospectively. In addition, the number of children in the 2 groups compared was not identical due to the fact that these are the only cases having benefited from a GeneXpert since its implantation in the hospital in 2019. As other limitation, we can mention monocentric nature of the study and also the small size of the sample. Thereby, a large-scale study should be carried out in order to have a reliable result that can be unanimously accepted.

CONCLUSION

The combination of clinico-radiological criteria is thus a more accessible means of individual diagnosis of pediatric TB in a low-resource country in the absence of reference methods.

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