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Screening of tuberculosis in highly exposed children in the population of Cameroon central region

Martine Augusta Flore Tsasse[1,2,3], Henry Dilonga Meriki[1], Henri Olivier Tatsilong Pambou[1], Hugues Clotaire Nana Djeunga[2], Ambe Marius Ngwa[1], Cyriaque Axel Ambassa[3,4]*, Jean Paul Assam Assam[3,5], Celine Nguefeu NKenfou[5,6], Véronique Penlap Beng[3,4], Joseph Kamgno[2,7], Patrick Nguipdop Djomo[2,8] and Jane Françis Tatah Kihla Akoachere[1]

[1]Department of Microbiology and Parasitology, Faculty of Science, University of Buea, Buea, Cameroon.
[2]Higher Institute for Scientific and Medical Research (ISM), Yaoundé, Cameroon.
[3]Laboratory for Tuberculosis Research and Pharmacology, Biotechnology Center, University of Yaoundé 1, Cameroon.
[4]Department of Biochemistry, Faculty of Science, University of Yaoundé I, Yaoundé, Cameroon
[5]Department of Microbiology, Faculty of Science, University of Yaoundé I, Yaoundé, Cameroon.
[6]Chantal Biya International Reference Centre, System Biology Laboratory, Yaoundé, Cameroon.
[7]Department of Public Health, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon.
[8]Faculty of Epidemiology and Population Health, London School of Tropical Medicine and Hygiene, London, United Kingdom.

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Although the treatment for tuberculosis (TB) is available nowadays, it remains a real concern, especially since cases in children are often detected late and underreported. Studies have shown that elevated serum levels of C-reactive protein (CRP) are associated with TB in adults. This study aims to assess the CRP levels among the pediatric cases at Jamot Hospital (Yaoundé) and Meguemessi community in Cameroon. This was a cross-sectional study that enrolled 97 participants aged 2 to 15 years between 2020 and 2023. Sputum was tested for active tuberculosis using Gene-x-pert and culture. Blood was collected to measure the CRP concentration levels using nephelometry and to screen for latent tuberculosis infection using Interferon Gamma Released Assay (IGRA). Amongst the 97 participants there were 7 confirmed cases of active TB, 27 cases of latent TB infection, and 44 healthy individuals (HI). The mean CRP levels for active TB, latent tuberculosis infected (LTBI), and HI were 110.81 ± 74.96, 7.76 ± 15.33 and 9.27 ± 15.57 mg/L, respectively. High levels of CRP were associated with active tuberculosis (p < 0.001). Serum CRP levels can provide valuable insight into the severity of the disease, making it a useful marker for early diagnosis, preventive therapy orientation and treatment of TB.

Key words: Active tuberculosis, latent tuberculosis infection, acute phase marker, C-reactive protein, contact children, central region, Cameroon.

INTRODUCTION

Tuberculosis continues to pose a significant public health threat worldwide, with an estimated 10.6 million new cases reported in 2021 (WHO, 2022). The burden of pediatric tuberculosis is substantial, with the World Health Organization (WHO) estimating that approximately 1.2 million children under the age of 15 fell ill with tuberculosis globally in 2021, resulting in approximately 200,000 deaths (WHO, 2022). Children aged 0-4 years, and those aged 5-14 years living with HIV, who live in the same household with an index tuberculosis patient are at an increased risk of progression to active tuberculosis disease, once infected (Fox et al., 2013; Du Preez et al., 2022). Furthermore, these children are more susceptible to severe forms of the disease, such as tuberculosis meningitis, and have a higher risk of mortality than other age groups (Du Preez et al., 2022; Marais et al., 2004). Household contact management (HCM) targets both pathways to improve tuberculosis control. It involves systematic tuberculosis screening for household contacts of patients newly diagnosed with tuberculosis (index patients) to identify and treat additional co-prevalent disease. Additionally, it provides tuberculosis-preventive treatment (TPT) to decrease tuberculosis risk in those without disease. Although only a minority of tuberculosis transmissions are believed to occur within households (Martinez et al., 2019), household contacts remain at a high risk of tuberculosis infection and disease in many settings (Velen et al., 2021). The WHO recommends systematic screening for tuberculosis in household contacts of individuals diagnosed with tuberculosis and tuberculosis preventive treatment initiation if eligible, with priority given to children under the age of 5 years and 5-14 years living with HIV (WHO, 2022). However, tuberculosis child contact management has not been routinely or effectively implemented in resource-limited settings due to multiple obstacles including healthcare system-related barriers such as infrastructure and human resources (Hwang et al., 2011; Tesfaye et al., 2020). Families also face several challenges in bringing children to the healthcare facility, including, among other things, the burden of travel, financial challenges, and transport costs (Szkwarko et al., 2020; Ayakaka et al., 2017). Active contact investigation at the community and household level, a key element of the family-centered care concept, is considered a critical intervention for enhancing both case finding and provision of TPT among children and adolescents (Yuen et al., 2022). It is difficult to collect sputum samples from infants and young children. In addition, the diagnostic tests used to detect mycobacteria in sputum are less likely to produce a positive result, which is explained by the fact that children are more likely to have tuberculosis caused by a smaller number of bacteria. Therefore, C-reactive protein is a promising acute-phase marker for the screening of active tuberculosis in an endemic setting.

CRP is a very sensitive marker for the acute phase response but cannot be used as specific diagnostic tool because of its non-specificity. Nevertheless, measurement of CRP in a patient's serum can provide useful information to clinician, as it is used as a marker of inflammation (Kashyap et al., 2020). In children with tuberculosis, serial estimation of CRP levels can provide a clue to the response of antitubercular therapy. Studies have shown that CRP levels rise with the onset of infection and fall significantly with clinical improvement, returning to normal levels when the inflammatory reaction subsides. It appears to be a suitable indicator of disease activity and if its level does not fall within 3-6 months of therapy, the patient should be reassessed to rule out progressive tuberculosis or treatment failure. Further evaluation of CRP by semi-quantitative, latex agglutination technique is quite rapid, giving result in 15 to 20 min and the test can be done in small laboratory and even in rural areas lacking newer technology. The objective of this study was to assess serum levels of CRP among the highly exposed pediatric population to tuberculosis infected individuals in the Centre region in Cameroon.

MATERIALS AND METHODS

Study design and participants

A prospective study was conducted among children aged 2 to 15 years old at Jamot reference hospital (Yaounde) and Meguemessi rural community (Akonolinga Health District) in the Centre Region, Cameroon between December 2020 and August 2023. Children aged two to fifteen years old were eligible for enrolment. Participants were grouped into three categories:

(i) The group of latent tuberculosis infected (LTBI) children, confirmed positive for whole blood Interferon Gamma Release Assay (IGRA), the Quanti FERON TB-Gold in Tube (GFT-GIT) (QIAGEN, Strasse 1, 40724 Hilden, Germany) and negative for TB symptoms. They were identified by liaising a pulmonary TB patient

*Corresponding author. E-mail: axel.ambassa@yahoo.fr.

(household contact) at tuberculosis treatment unit from Jamot reference hospital (urban area);
(ii) The second category was healthy individual (HI) randomly recruited in the Meguemessi rural community (Akonolinga Health District), negative for IGRAs;
(iii) The third category were children with confirmed active tuberculosis (ATB) recruited from the Jamot hospital before the beginning of treatment or within one week of anti-tuberculosis drug initiation. This third category were children with at least two of the following clinical manifestations (a) a cough for at least two weeks; (b) unexplained weight loss or failure to thrive; (c) unexplained diminished playfulness for at least 1 week; (d) an abnormal chest-X Ray (CXR). All ATB children were found positive by GeneXpert MTB/RIF and culture. All participating children underwent a CRP testing.

Clinical procedures

Demographic and clinical questionnaires were administered and standard TB evaluation including a physical exam was performed, as well as CXR and microbiology testing (children presenting clinical characteristic of TB). Expectoration specimen was collected for molecular testing with Xpert MTB/RIF Ultra test (Cepheid), acid fast bacilli (AFB) smear microscopy and AFB culture. In addition, 5 mL of blood was collected in the heparin tube for later diagnosis of latent tuberculosis infection, excluding children with identified TB signs. Volumes of 2 to 3 mL of blood were collected from each of the participants. After centrifugation, serum was separated and stored at -60°C until further use to CRP levels determination. The test was performed using commercially available high sensitivity C-reactive protein assay (Genrui Biotech, Shenzhen, China). The decision regarding initiation of preventive therapy or anti-TB treatment was made by TB clinic staff in accordance with Cameroon National Guideline (PNLT, 2019).

TB testing procedure

All tests were performed at the Centre Pasteur of Cameroon laboratory in accordance with standard protocols [Reference]. GeneXpert, microscopy, culture was performed on solid media: Löwenstein Jensen (LJ) and Löwenstein Jensen containing 0.4% of sodium pyruvate solution (Narvaiz de Kantor et al., 1998; Niobe-Eyangoh et al., 2003; Assam et al., 2013; Koro et al., 2016).

LTBI testing

LTBI was performed by Interferon Gamma Released Assay (IGRA) according to the manufacturer instruction, QuantiFERON TB Gold in Tube (QIAGEN, Strasse 1, 40724 Hilden, Germany) and positivity was defined as an interferon gamma concentration (IFN-γ) equal to or higher to 0.35 IU/mL.

C-reactive protein (CRP) testing procedure

The concentration of CRP was measured by nephelometry with PA54 protein analyzer and CRP Detection Kit Reagent (Genrui Biotech Inc, Shenzhen, China). The test's detection range was 3 to 300 mg/L.

Ethical considerations

Written informed parental consent was obtained for all children enrolled in the study as well as assent for participants 12 years and older. The study was approved by the Human Health Research Council Ethics Committee of Centre Regional Cameroon (EC N°1903/CRERSHC/2020), the Jamot Hospital authority and the Akonolinga Health District authority.

Statistical analysis

The statistical analysis was conducted using R software version 4.1.3 (R Core Team, 2021). Demographic and clinical characteristics were summarized using descriptive statistical analysis. The differences in CRP markers were analysed among active TB, LTBI, and healthy individuals (HI), and 95% confidence intervals were calculated. Non parametric tests as the Kruskal-Wallis test was performed to compare the three groups (Guo et al., 2013), and the Mann-Whitney U test (Guo et al., 2013) was used for comparisons between two groups. Additionally, a receiver operator characteristic (ROC) curve analysis (Xavier et al., 2011) was performed to verify the clinical utility of the results and to determine the cut-off value, specificity, and sensitivity of the assays (Shi et al., 2022; Kang et al., 2022). The statistical significance was considered for p-values less than 0.05. All data obtained and reported here were treated anonymously by the investigators.

RESULTS

Demographic and clinical characteristics of the study participants

A total of 97 children were enrolled into the study. Of this study participants, 44 (45.4%) were healthy control; 7 (7.2%) were confirmed TB patients, among which, 1 case was of extra pulmonary TB; 46 (47.4%) were children contact of pulmonary TB cases in household. From 46 children contact to index case, 27 (58.2%) had latent TB. Age group 2 to 5 years old (40.2%) were highly represented as well, and the female gender was most represented (54.6%). The detailed characteristics of the study participants are shown in Table 1.

Quantitative CRP analysis results for the active TB, LTBI and healthy individuals

The mean CRP values for the active TB, LTBI, and healthy individuals (HI) were 110.81 ± 74.96, 7.76 ± 15.33, and 9.27 ± 15.57 mg/L, respectively (Table 2). Individuals with active tuberculosis (ATB) exhibited significantly higher CRP levels compared to both HI and those with LTBI (Chi square = 20.434, $p < 0.001$, df = 2). ATB had significantly higher CRP serum level than LTBI ($p < 0.001$). A similar result was obtained when ATB was compared to HI ($p < 0.001$). Notably, CRP levels in LTBI individuals were not significantly different from those in

Table 1. Clinical characteristics of the study subjects.

Variable	Totals (%)	Total ATB cases (%)	Total TB contact cases (%)	Total healthy individuals (%)
Age group (years)				
[2-5]	39 (40.2)	1 (14.3)	20 (43.5)	18 (40.9)
[6-10]	32 (33)	2 (28.6)	14 (30.4)	16 (36.4)
[11-15]	26 (26.8)	4 (57.1)	12 (26.1)	10 (22.7)
Gender				
Female	53 (54.6)	5 (71.4)	25 (54.3)	23 (52.3)
Male	44 (45.4)	2 (28.6)	21 (45.7)	21 (47.7)
AFB microscopy				
Negative	1 (16.7)	1 (16.7)	NA	NA
Positive	5 (83.3)	5 (83.3)	NA	NA
AFB culture				
Negative	0 (0)	0 (0)	NA	NA
Positive	6 (100)	6 (100)	NA	NA
MTB_PCR				
Négative	0 (0)	0 (0)	NA	NA
Positive	6 (100)	6 (100)	NA	NA
IGRA_Test				
Negative	62 (68.9)	NA	19 (41.3)	43 (97.7)
Positive	28 (31.1)	NA	27 (58.7)	1 (2.3)

NA: Not applicable (not done). MTB: Mycobacterium tuberculosis, IGRA: Interferon Gamma Release Assay, AFB: Acid Fast Bacilli, PCR: Polymerase Chain Reaction.

the healthy group (p = 0.4035) (Figure 1 and Table 2). These findings suggest a strong association between active tuberculosis and high systemic inflammation, as indicated by CRP, while latent infection appears to have minimal impact on CRP levels.

An analysis of the receiver operator characteristic (ROC) curve based on the results of CRP

The ROC curve analysis was performed to assess the clinical usefulness of the CRP results. The Area under the receiver operating characteristic curve (AUC) for CRP was found to be 94.7% (95% CI: 87.5 - 100) (Figure 2 and Table 3). The best cut-off value of 3.291 mg/L was obtained. The optimum cut-off point was calculated where sum of sensitivity and specificity was maximum (sensitivity 100%; specificity 80.0%). Thus, AUC of serum CRP levels was found to significantly discriminate between ATB and healthy children ($p < 0.001$). At a threshold of 0.5 mg/L, CRP has lower sensitivity (71.4%) but higher specificity (100%). This means that the test may not detect all cases of TB, resulting in false negatives, but it will accurately identify all healthy individuals, avoiding false positives.

To investigate the relevance of the CRP, the area under the receiver operating characteristic curve (AUC), the sensitivity and the specificity will be analysed (Table 3).

DISCUSSION

A biomarker-based triage test that can be performed in primary care clinics to assess the outcome of household TB+-contact is needed for children. This test should be rapid and efficient. Although CRP has shown promise for TB triage among adults living with HIV and correlates with other host gene expression signatures for TB diagnosis (Yoon et al., 2017; Södersten et al., 2021), we

Table 2. Acute-phase protein levels in serum samples between ATB (active tuberculosis), LTBI (latent tuberculosis infected), and HI (healthy individual).

N (number of participants) C-reactive protein (mg/L)	ATB 7	LTBI 27	HI 43
Median	152.42	3	3
Mean	110.81	7.76	9.27
SD	*74.96*	*15.33*	*15.45*

SD: Standard deviation (n=77).

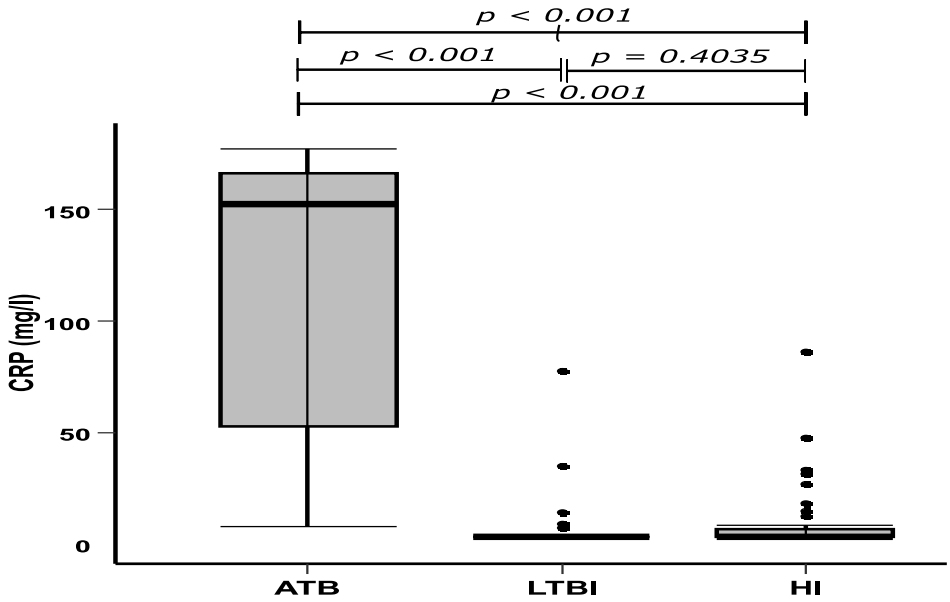

Figure 1. Comparison of C reactive proteins (CRP) between the different groups of patients studied: active tuberculosis (ATB), latent tuberculosis infected (LTBI) children, and healthy individual (HI).

found that CRP levels had limited performance in discriminating between TB disease and LTBI in children. Our findings indicate that CRP has a limited role in triaging latent TB Infection in children at the point of care. In 2012, WHO first recommended Household Contact Management for children under 5 years old and people living with HIV (WHO, 2012). This recommendation was later expanded to include all child contacts under 15 years old (WHO, 2018). However, global coverage of TPT in children younger than 5 years remains low. As of the end of 2022, only 55% of the target of 4 million set for the 2018 to 2022 period by the UN General Assembly high-level meeting on tuberculosis had been reached according to WHO (2023).

This study included mostly female children, with 40.2% under the age of 5. Of the total, 47.4% were children who had been in contact with pulmonary TB cases in their household, 45.4% were healthy controls, and 7.2% were confirmed TB patients. Among the 46 children who had been in contact with the index case, 58.2% had latent TB. It is crucial to manage TB effectively to differentiate between LTBI and active TB and to identify the appropriate anti-TB treatment. Currently, either the TST or IGRA test is used to diagnose latent tuberculosis infection (LTBI) (Sharma et al., 2017). It is important to note that a single test can lead to erroneous diagnoses of both LTBI and active TB (Mamishi et al., 2019).

CRP values for individuals with active TB, LTBI, and without TB (healthy individuals (HI)) were 110.81 ± 74.96, 7.76 ± 15.33, and 9.27 ± 15.57 mg/L, respectively. CRP levels were notably high in children with confirmed TB. This high CRP level is a profile of post-primary TB (De Beer et al., 1984). Generally, in primary paediatric TB, the CRP level is very low (Zitrin, 1960; Albuquerque et

Table 3. The diagnostic utility of CRP marker for tuberculosis (ATB).

Parameter	AUC% (95% CI)	Cut-off value	Sensitivity % (95% CI)	Specificity % (95% CI)	*P*-value
CRP	94.7 (987.5-100)	3.2	100 (100-100)	80 (70-88.7)	<0.001

CI: Confidence interval.

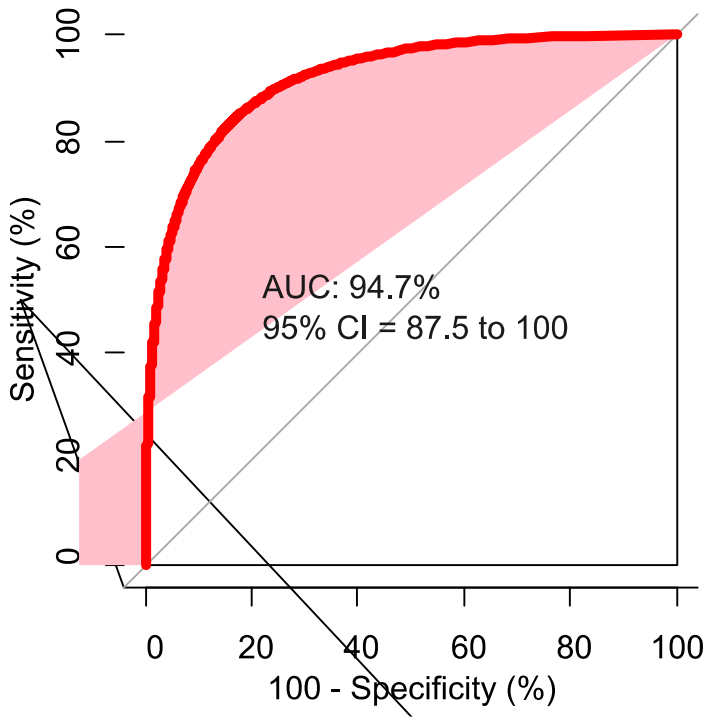

Figure 2. ROC curve analysis for serum levels of CRP among the ATB participants and healthy individuals.

al., 2019; De Beer et al., 1984). The studies that have shown CRP elevation in paediatric TB have mainly involved older children who are more likely to have post-primary TB (Herlina et al., 2011; Kashyap et al., 2020). This study suggests that higher CRP levels in children with TB may be related to post-primary disease rather than primary TB, as is the case in younger children. Similar observation were made in a study conducted in South Africa which compared CRP levels in children with primary TB, adolescents and adults with no lung destruction, and adults with post-primary TB with lung destruction (De Beer et al., 1984). During primary tuberculosis, *M. tuberculosis* spreads through the lymphatic system and is less likely to cause extensive lung damage and cavitation (Starke and Donald, 2016), resulting in a less robust acute phase response. It is important to note that the immune response to TB differs between children and adults (Basu et al., 2019), which may affect CRP levels.

The ROC curve analysis was performed to assess the clinical usefulness of the CRP results. The area under the receiver operating characteristic curve (AUC) for CRP was found to be 94.7% (95% CI: 87.5 - 100). The data showed a significant increase in CRP values ($p < 0.0001$, AUC = 94.7%) in the active TB group compared to the LTBI group and healthy individuals. Although numerous studies have been conducted, a gold standard that can differentiate between active TB, LTBI and healthy individuals groups does not exist. This study thus aimed to compare the CRP levels in serum samples to differentiate between active TB, LTBI and healthy individual groups and ultimately identify as biomarkers that can be used to differentiate LTBI from active TB.

However, this study presents some limitations. Firstly, the sample size was small, due to missed appointments caused by poor network coverage and the unavailability

of children's caregivers. To validate the significance of the results reported in this study and to improve the accuracy of discriminating between the active tuberculosis and latent tuberculosis-infection groups, a study with a larger number of contact cases and a larger population of children under 15 years of age is necessary.

Conclusion

In Cameroon a significant number of pediatric TB cases and LTBI remain undiagnosed due to the lack of a gold standard. Tuberculosis is often diagnosed based on clinical and radiological criteria along with medical history. Although CRP is a non-specific marker of inflammation, it can significantly differentiate between pediatric TB cases and healthy controls. The use of this tool may be incorporated into the algorithms for diagnosing pediatric tuberculosis, along with clinical history, microbiology, radiology, and tuberculin skin tests. It has the potential to be an important tool in ruling out tuberculosis in children.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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