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ORIGINAL ARTICLE

Diagnosis of tuberculosis in children: the role of hemogram and inflammatory markers

Tyane de Almeida Pinto¹, Andrea Maciel de Oliveira Rossoni^{2,3}, Cristina de Oliveira Rodrigues⁴, Marssoni Deconto Rossoni^{3,5}, Tony Tannous Tahan^{2,4}

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Abstract

It is known that childhood tuberculosis (TB) is a global public health problem, although the diagnosis and treatment of TB are neglected. Few cases are confirmed by laboratory tests because TB is paucibacillary in childhood. Therefore, clinical, epidemiological, radiological, and laboratory criteria are used for diagnostic confirmation. This study reviews the literature to determine the role of hemogram and tests of inflammatory markers in diagnosis. Few studies have addressed this subject and the most common findings in the hemogram are anemia of chronic disease (normochromic and normocytic) with a non-specific leukogram and platelet disorders. The most important factor in the clinical suspicion of TB may be the absence of leukocytosis, which is common in acute febrile respiratory illnesses. The levels of inflammatory markers are usually high, but some studies question the value of ESR for the diagnosis of TB. Future studies will help confirm the usefulness of other laboratory parameters in the screening and diagnosis of TB in children.

¹ Resident Physician in Pediatric Infectology - Clinics Hospital Complex, Federal University of Paraná [Complexo Hospital de Clínicas, Universidade Federal do Paraná (CHC - UFPR)].

² Physician at the Pediatric Infectology Service of the CHC - UFPR.

³ Professor at the Department of Medicine - Federal University of Ponta Grossa.

⁴ Professor at the Department of Pediatrics - UFPR.

⁵ Professor at the Department of Clinical Medicine - UFPR.

Correspondence to:

Andrea Maciel Oliveira Rossoni.

Rua Gen. Carneiro, nº 181, Alto da Glória. Curitiba - PR, Brazil. CEP: 80060-900. E-mail:

INTRODUCTION

Tuberculosis (TB) is a global public health problem. Each year, approximately 70,000 new cases are reported in Brazil with high mortality rates in adults and children. According to 2016 data from the Ministry of Health (MS), the incidence of TB in Brazil was reduced by 20.2% between 2006 (38.7 per 1,000 inhabitants) and 2015 (30.9 per 1,000 inhabitants), and the mortality rate was reduced by 21.4% from 2004 (2.8 per 100,000 inhabitants) to 2014 (2.2 per 100,000 inhabitants)¹. Despite these advances, many challenges remain to reach the ultimate goal of eliminating TB: a 90% reduction in the rate of incidence and a 95% reduction in the coefficient of mortality by 2035¹.

In 2016, the World Health Organization estimated one million cases of tuberculosis in the pediatric age group (children younger than 15 years of age) worldwide, accounting for 10% of the total cases, and 210,000 deaths in 2015². In high-burden countries, including Brazil, the occurrence of TB in children younger than 15 years is estimated to represent more than 10% of the total cases³. However, the data from the Brazilian MS for 2106 indicated that only 3.2% of the reported cases were diagnosed in children⁴.

Although children account for 10% to 20% of the global TB burden, diagnosis and adequate therapeutic formulations are still neglected for this age group³.

Cases of pediatric TB are probably underreported because of the difficulty in diagnosis. Childhood TB is paucibacillary, which limits laboratory confirmation. Therefore, diagnosis is based on a combination of clinical, epidemiological, radiological, and laboratory criteria. The combination of several of these criteria is normalized in Brazil using a point score system, which defines the probability that a certain condition is due to TB and guides the treatment or investigation of new pathologies⁵.

The most used criteria in diagnosis are clinical symptoms suggestive of TB, history of contact with infected adults, reactive tuberculin test, and radiological changes. Non-specific complementary laboratory tests are not diagnostic criteria for TB; however, whether these tests can assist in diagnosis is still unknown.

This study reviews the literature and describes the implications of hemogram and the tests of inflammatory markers on the diagnosis of TB in children.

LABORATORY CHANGES - HEMOGRAM

Various hematological changes associated with TB have been described. The most common findings are normochromic and normocytic anemia of chronic disease⁶ and reduction in the total number of erythrocytes⁷.

The leukogram varies and may reveal neutropenia, leukopenia, lymphopenia, lymphocytosis, and monocytosis⁶. Lymphopenia may appear in acute cases and monocytosis may occur during disease evolution. The most important criterion

may be the absence of significant leukocytosis in an acute respiratory profile, which could suggest the occurrence of TB. However, the contribution of these changes to diagnosis is limited because of the lack of specificity⁸.

With regard to platelet count, there is an association between thrombocytosis and active TB⁹. Sahin et al.⁹ compared patients with pulmonary TB and bacterial pneumonia and healthy controls and demonstrated this change in 44% of the patients in the TB group, with statistical significance compared with the other groups. It has been shown that platelet microthrombi are formed in the cavitations caused by TB as a defense mechanism in adults. Radiographic images showed that only thrombocytosis was associated with a greater extension of the lesion.

The mean platelet volume was lower in patients with TB but did not reflect severity, and thus the use of this variable is not recommended as a marker in the acute phase of TB¹⁰. However, in some cases, such as in disseminated or miliary TB, thrombocytopenia may occur, as described by Singh⁶.

An uncommon change in the hemogram is pancytopenia, which characterizes the hemophagocytic syndrome when associated with fever, splenomegaly, and hyperferritinemia, and can be triggered by TB. Although it is classically associated with Epstein-Barr virus and cytomegalovirus, new cases associated with TB have been reported^{11,12}. Changes in the coagulogram may occur in these cases¹³. Therefore, the diagnosis of this condition should always be considered, particularly in patients with a poor response to TB treatment, taking severity into account¹¹⁻¹³.

All the changes in the hemogram are usually resolved with anti-tuberculostatic treatment⁶.

LABORATORY CHANGES - TESTS FOR INFLAMMATORY MARKERS

In patients with active TB, there is an association with acute-phase reactants - erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)^{7,9}. However, what has historically been recognized as effective in predicting this diagnosis has now been questioned.

Studies in adults reported an increase in the ESR of up to 99% in cases of TB. However, the accuracy of this test is low because of the positivity for other diseases other than TB. Moreover, the increase in ESR may be absent in children with TB¹⁴.

Al-Marri and Kirkpatrick¹⁵ evaluated the ESR results of all cases of TB in children aged 14 years or younger recorded in the National Program of Qatar from 1983 to 1996. These authors found that the ESR was significantly higher in symptomatic children and in those with a positive culture. There were no differences in the location of TB (pulmonary or extrapulmonary), patient age, or the reactivity of the tuberculin test. By contrast, there were significant variations among individual ESR values, with a considerable overlap. The

presence of infected children with normal test results and normal children with positive test results limit the assessment of the usefulness of individual patient results in the diagnosis of TB.

Niu et al.¹⁶ compared procalcitonin, CRP, interleukin-10, and ESR in adults with acute bacterial pneumonia and adults with pulmonary tuberculosis and concluded that the levels of procalcitonin, CRP, and interleukin-10 were higher in patients with pneumonia than in those with TB, whereas the ESR was equally high for both diseases. However, these authors observed that the ESR was associated with TB activity and was the parameter more strongly associated with TB among the studied parameters. The sensitivity and specificity of procalcitonin was higher in all tests. Notwithstanding, the authors suggested that new studies be developed to confirm these findings.

The successful use of several electrolytes has been reported. Luterotti et al. evaluated the possibility of use of zinc and copper levels as follow-up parameters to assess the persistence or recurrence of infection but concluded that the variations in the levels of these metals were not specific to TB¹⁷.

FINAL CONSIDERATIONS

It is known that TB is endemic in Brazil and many children are underdiagnosed. Diagnostic confirmation is difficult in children primarily because they are paucibacillary. Few studies have evaluated the changes in the hemogram and inflammatory markers in TB.

The hemogram shows normochromic and normocytic anemia, in addition to non-specific changes in the white series. There appears to be an association between thrombocytosis and active TB. The standalone ESR is not very important for diagnosis. However, a high ESR associated with suggestive symptomatology can help the diagnosis. In addition, more studies are necessary to elucidate the role of other inflammatory markers, including CRP, procalcitonin, and IL-10.

New studies on the positive and negative predictive scores of these diagnostic tests should be conducted.

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