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Clinical and immunologic characteristics of tuberculosis: comparison between children and adults

Características clínicas e inmunológicas de tuberculosis: comparación entre niños y adultos

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ABSTRACT. Pulmonary tuberculosis (PTB) remains a global public health problem, despite the efforts made in programs to eliminate it, the goals have not been attained, partially due to limitations in the time of diagnosis of the disease, which allows transmission to others. PTB is an infectious disease that infects people of all ages, when diagnosing PTB in children, it is necessary to take into account the age-specific characteristics of the disease, since although the risk of PTB is higher in younger infants, from the age of five the risk decreases, they have a functional immune response similar to that of adults and it must be taken into account that transmission in children is usually by close contact with an adult patient with PTB. The diagnosis of TB in children and adults is based on a combination of clinical, radiological, microbiological and immunological findings. In this review we identify the main clinical differences that occur in children and adults with TB and the differences between clinical guidelines and research reports, as well as immunological findings that could have an application in timely diagnosis.

Keywords: pulmonary tuberculosis, diagnosis, clinical features, immunologic features.

RESUMEN. La tuberculosis pulmonar continúa siendo un problema de salud pública a nivel global, a pesar de los esfuerzos en programas para eliminarla, las metas no se han alcanzado, en parte por las limitaciones en el tiempo del diagnóstico de la enfermedad, lo que permite la transmisión a otras personas. La tuberculosis pulmonar es una enfermedad infecciosa que infecta a las personas de todas las edades, pero en particular cuando se trata de diagnosticar tuberculosis pulmonar en niños, es necesario considerar las características específicas de la edad, ya que mientras el riesgo de tuberculosis pulmonar es mayor en los lactantes más pequeños, a partir de cinco años disminuye el riesgo, ya que poseen una respuesta inmunitaria funcional similar a la de los adultos y se debe tomar en cuenta que la transmisión en niños generalmente es por contacto estrecho con un paciente adulto con tuberculosis pulmonar. El diagnóstico de la tuberculosis en niños y adultos se basa en una combinación de hallazgos clínicos, radiológicos, microbiológicos e inmunológicos. En esta revisión identificamos las principales diferencias clínicas que se presentan en niños y adultos con tuberculosis y diferencias entre las guías clínicas y los reportes de investigación, así como los hallazgos inmunológicos que podrían tener una aplicación en el diagnóstico oportuno.

Palabras clave: tuberculosis pulmonar, diagnóstico, características clínicas, características inmunológicas.

INTRODUCTION

Tuberculosis (TB) is a disease spread through the air that can infect people of all ages. Because of the route of transmission, pulmonary tuberculosis (PTB) is the most common clinical form. The World Health Organization (WHO) estimates that 10.0 million people were infected with TB in 2019, of which 56% are adult men (≥ 15 years), 32% adult women (≥ 15 years) and 12% are children (< 15 years).[1] In an *M. tuberculosis* infection there are differences

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in bacillary load, diagnosis, disease spectrum, risk factors and clinical characteristics that vary according to the age of the infected subjects.[2,3]

Neonates (0-12 months) and infants (12-24 months) are five to 10 times more likely to progress to active TB after infection, and are also more likely to develop severe and disseminated forms of the disease. Most adults are able to contain *M. tuberculosis* without developing active disease or eliminating the microorganism and it is estimated that only 5-10% of infected people will develop active TB.[4] Age and maturation of the immune system are major promoters involved in the development and phenotype of TB infection. Changes in risk and disease development have been observed at different stages of growth *(Table 1)*.[5,6]

CLINICAL MANIFESTATIONS OF PULMONARY TB IN CHILDREN AND ADULTS

Adults and children with PTB show varied and distinct clinical manifestations. In children, clinical diagnosis is chosen over microbiological diagnosis, and although most cases have no signs or symptoms, it is estimated that a diagnosis is only achieved in 70% of cases.[7] Contact with a person with TB, contact history, is one of the most important factors in the clinical diagnosis of PBT in children.[8] In the case of adult contact with PTB, signs and symptoms may be common with other respiratory infections, making timely diagnosis and treatment of PTB difficult.[6] Children 5 to 10 years of age may have clinically silent disease while children under two years of age are more likely to have signs and symptoms of lung disease.[9-11] Some common constitutional symptoms include decreased appetite (alteration of weight percentiles in children under 15 years of age), fatigue, and fever *(Table 2)*.[11-13]

In infected adults, the signs and symptoms are clearer, among the main clinical manifestations are: fever, loss of appetite (weight loss), asthenia, profuse night sweats and general malaise. A special form of onset is tuberculous pneumonia, which may present as a radiological clinical manifestation similar to that of bacterial pneumonia *(Table 2)*.[6,8,13-16]

The WHO establishes a cough of any duration as a sign of PTB, in recent reports chronic and incessant cough that does not improve in more than three weeks, ruling out other causes, is mentioned; however, the Clinical Practice Guide mentions productive cough greater than two weeks, this being the only relevant clinical difference by time of evolution, in addition the information on signs and symptoms is scarce in children with TB who become the most affected by treatment.

DIAGNOSIS OF PULMONARY TB IN CHILDREN AND ADULTS

It is estimated that TB in all its forms affects up to a quarter of the world's population,[16] and that the disease of PTB is mostly underestimated in children, these data represent a challenge for the timely diagnosis of PTB. That is why the variety of signs and symptoms that occur, as well as the absence of these, should be evaluated and clinical data explored in the primary caregiver or the history of recent contacts.[11,17,18] The difficulty in establishing a definitive diagnosis, coupled with the frequency of extra pulmonary disease in young children, makes the public health priority lower than in adults.[19-22]

The diagnosis of PTB is based on multiple modalities, including clinical, radiological and bacteriological data. Clinically, children have forms of paucibacillary PTB (few *M. tuberculosis* bacilli) or extra pulmonary TB.[11,23,24] In neonates to school children (0-10 years) TB diagnostic tests are usually performed using invasive procedures.[25] For both adults and children we can include imaging studies such as chest radiography, which is commonly the most informative research, although there are significant differences, among which we can find according to age, high-resolution chest computed tomography (CT) that provides more accurate visualization, but its use should be limited to complicated cases.[11,18,25,26]

Microbiological diagnosis is limited by the difficulty of obtaining sputum samples in children, since they can rarely provide a sample of expectorated sputum, coupled with the fact that children produce few bacilli, makes microbiological isolation for bacilloscopy tests not very sensitive, the

Table 1: Risk of developing active tuberculosis (TB) at different stages of growth.[5,6]

	Age (%)					
	Young neonatal-infant	Older infant	Preschoolers	Schoolchildren	Adolescent	Adults
Pulmonary TB risk	30-40	10-20	5	2	10-20	5-10
Extrapulmonary TB risk	10-20	2-5	0.5	< 0.5	< 0.5	< 0.5

Young neonatal-infant: 0-12 months old. Older infant: 12-24 months old. Preschoolers: 2-5 years of age. Schoolchildren: 5-10 years of age. Adolescent: 11-19 years of age. Adults: 19 years of age and older.

Table 2: Tuberculosis (TB) clinical manifestations, signs and symptoms in children and adults.[6,8,11-16]

	Reports		Clinical Practice Guide		WHO consolidated guidelines on tuberculosis 2022. Diagnosis and treatment	
	Signs	**Symptoms**	**Signs**	**Symptoms**	**Signs**	**Symptoms**
Children	Lost of weight*	Night sweats	Lost of weight*	Weakness o fatigue	Lack of weight gain Delayed growth	Night sweats
	Fever of > 38 °C during at least two weeks, ruling out other common causes	Non-specific toxic signs	Fever	Lack of appetite	Fever	—
	Chronic and incessant cough that does not improve ≥ 3 three weeks	Signs of hypersensitivity such as erythema nodosum	Productive cough ≥ 2 weeks	—	Cough of any duration Chest pain Hemoptysis	—
	Wheezing Neonatal and infants: common Preschoolers and schoolchildren: uncommon	—	—	—	Dyspnea	—
Adults	Productive cough ≥ 2 weeks	Shivers	Productive cough ≥ 2 weeks	Night sweats	Cough of any duration	Night sweats
	Hemoptysis	Lack of appetite	Hemoptysis	Lack of appetite	Hemoptysis Chest pain Dyspnea	—
	Fever**	Fatigue	Fever	Fatigue General malaise	Fever	—
	Lost of weight	—	Lost of weight	—	Lost of weight	—

* According to the child's growth curve and percentile chart. ** Greater than 38.3 °C. Data from other Clinical Practice Guide reports.
World Health Organization (WHO) Consolidated Guidelines on Tuberculosis. Module 3: Diagnosis and treatment. Rapid diagnostic means for the detection of tuberculosis.

culture of *M. tuberculosis* only detects about 30-40% of cases in children.[7] So smear microscopy has been replaced by smear tests nucleic acid culture and amplification in children.[26,27] Although the WHO recommends the use of the Xpert MTB/RIF test for all children suspected of TB,[15] other studies show that the diagnostic value of the Xpert MTB/RIF in bronchoalveolar fluid (BALF) samples in patients with PTB has a high sensitivity and specificity, except for children.[28,29] In another study in children under 15 years of age, the Gene Xpert MTB/RIF test showed a sensitivity of 50% and a specificity of 96% in samples of gastric lavage, induced sputum and BALF, with a higher sensitivity than bacilloscopy.[30] Due to the above, molecular tests should be considered as a diagnostic tool in children without ruling out follow-up in children with negative tests.

In adults, the diagnosis is usually more timely and is based on microbiological tests such as bacilloscopy and the culture of *Mycobacterium tuberculosis* (*M. tuberculosis*), with the culture of *M. tuberculosis* being the gold standard test.[7,8] There are different diagnostic methods according to age, according to current reports and the Clinical Practice Guide *(Table 3)*.[8,11,15-17,31-34] Signs, symptoms and type of diagnosis may vary depending on age *(Figure 1)*.[1,6,7,9-11,24,26,31,35-37] Over time, more complex diagnostic methods have been developed and improved that allow us to approach the patient in a timely manner to carry out an adequate

Table 3: Diagnosis with chest X-ray, TST, nucleic acid amplification and IGRA in children and adults.[8,11,15-17,31-34]

	Data from other reports	Clinical Practice Guide	WHO consolidated guidelines on tuberculosis 2022. Diagnosis
Children	**Normal or lateral chest X-ray**		
	A primary complex, consisting of: opacification (mediastinal or subcarinal) and consolidation or a segmental lesion (infiltrate and atelectasis)	With unilateral infiltrate or pleural effusion not explainable by another cause	It has poor specificity and therefore very low performance for true positive TB
	Sputum bacilloscopy		
	Induction of sputum (warm saline) in cases of sampling is difficult.	In sputum and gastric juice with the disadvantage that it is paucibacillary	Basic diagnostic test, not very sensitive
	Tuberculin skin test		
	Immunocompromised children (including HIV positive children): > 5 mm and in all other children (with or without BCG vaccine): > 10 mm	Exposed to adults with active PTB ≥ 10 mm	> 5 mm in children with severe malnutrition, > 10 mm children exposed to adults with TB
	Xpert MTB/RIF or Xpert Ultra		
	Xpert MTB/RIF in pulmonary TB, and extrapulmonary detects 80%	It does not mention information about it	The Xpert Ultra test should be used as the initial diagnostic test for TB
	IGRA in children		
	It is limited, of low quality, little evidence of studies in neonates and schoolchildren. In children with HIV, sensitivity is low	It does not mention information about it	In children over 2 years of age
Adults	**Normal or lateral chest X-ray in adults**		
	Hilarlymph adenopathies, pleural effusion	Pulmonary consolidation, fibrous changes on chest X-ray suggestive of inactive PTB	Extensive cavernous disease may occur. It offers high sensitivity, but low specificity
	Sputum bacilloscopy in adults		
	Recommended, with 73% sensitivity	Rapid study, sensitivity (51.8%), specificity (97.5%) Nebulization with hypertonic sterile saline solution (3%) where it is not possible to obtain a sample spontaneously	It is a basic diagnostic technique It is not a very sensitive test Recommended for monitoring patients with treatment
	Tuberculin skin test in adults		
	People without risk factor: > 15 mm People where TB is endemic: > 10 mm People with recent contact or HIV: > 5 mm	≥ 10 mm or ≥ 5 in: close contact with active TB case, HIV, immunocompromise, corticosteroid use, immunosuppressive therapy	> 5 mm in recent contact with TB, > 10 mm in: injecting drug users, residents of high-risk groups * and > 15 mm in people without risk factors for contact with TB
	Xpert MTB/RIF in adults		
	High specificity (85-98%) High sensitivity for TB with positive bacilloscopy (96%) Lower sensitivity for TB with negative bacilloscopy (66%)	It does not mention information about it	It should be used as the initial TB diagnostic test and detection of rifampicin resistance
	IGRA in adults		
	> 95% specificity and better sensitivity when combined with TST	It does not mention information about it	Decreases exposure to TB preventive treatment

TST = tuberculin skin test. IGRA = interferon gamma release assays. WHO =World Health Organization. TB = tuberculosis. HIV: human immunodeficiency virus. PTB = pulmonary tuberculosis. BCG = bacillus Calmette Guerin.
* People who are in jail, recent immigrants from countries that have a high TB burden.

treatment, although they also allow us to see that we still have a long way to go with the diagnostic methods used in children in PTB, which is complicated due to its variety of presentation and the damages that anti-tuberculosis drugs can generate in minors. This advancement of diagnostic methods has outpaced the Clinical Practice Guideline due to a lack of up-to-date information *(Figure 1 and Table 3)*.

The variety of signs and symptoms that patients may present according to the stage in which they are, together with the diagnostic methods that could be employed according to age, are shown in *Figure 1*.

As an alternative, different evaluations of both the hematological populations and the immune response of the host in response to *M. tuberculosis* infection have been proposed, which may be complementary to the diagnosis of TB and/or the follow-up of pharmacological therapy, although they are not routinely performed.[38]

HEMATOPOIETIC POPULATIONS IN CHILDREN AND ADULTS

Because hematologic populations vary with age, reports of hematologic counts from healthy subjects compared to patients with PTB at different ages were analyzed. In neonates, the immune system is in an immature state, which develops during the first years of life. The maturation of the immune system will depend in part on antigen exposure. This is why both children and older adults are more susceptible to infections in general.[39,40] Although some patients may have variations in the absolute numbers of hematologic subpopulations, when these values are compared in patients with PTB without comorbidities such as HIV, the number of hematologic cells is not significantly different in the different groups *(Table 4)*.[41-45]

Overall, monocyte, lymphocyte, and eosinophil counts in TB patients are within the normal range relative to healthy controls; however, in some patients, hematological alterations such as monocytosis, eosinophilia, lymphopenia, and neutrophilia have been reported,[5,46] some of these alterations have been associated with HIV co-infection.[43]

It is unclear how much variations in hematological values contribute to TB. What has been observed to a greater extent is susceptibility to TB in children attributed to an immature immune status.[47]

IMMUNODIAGNOSIS OF PULMONARY TB IN CHILDREN AND ADULTS

Because existing conventional diagnostic methods are often limited in time to diagnosis, sensitivity, and/or specificity, and are sometimes too costly or complex for resource-limited settings,[25,48] immunological studies based on host response to *M. tuberculosis* infection have been conducted, predicting treatment efficacy, reactivation of infection, and immune responses by vaccination.[49] Over the past few decades, different host response-based markers (biomarkers) have been proposed for the diagnosis of PTB, which have focused on diagnosing active PTB, latent TB, and measuring the efficacy of treatments.[38,49]

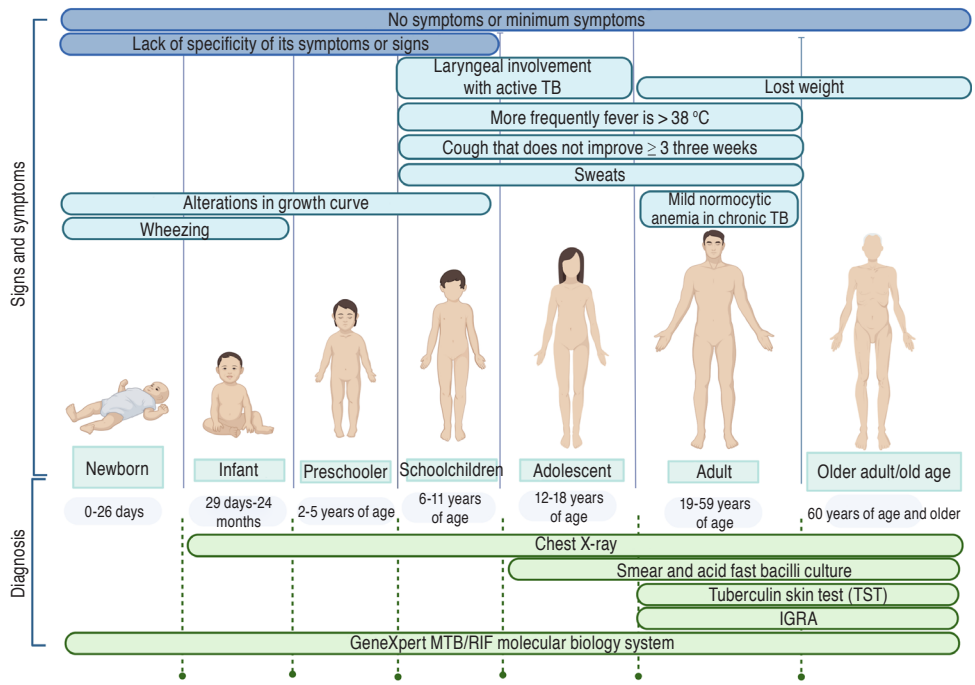

Figure 1:

Signs, symptoms and diagnostic according to age for pulmonary tuberculosis.[1,7,10,17,26,28,34,38-43]

Table 4: Comparison of hematopoietic cell counts in healthy and tuberculosis patients during neonatal-preschoolers and adult age.[5,41-47]

Cells	Condition	Neonatal-preschoolers* (× 10^3/mm^3)	Adolescents-adults** (× 10^3/mm^3)
Monocytes	Healthy	0.5-1.1	0.3-1.1
	Tuberculosis	0.83	0.41-0.69
Neutrophils	Healthy	1.5-8.5	1.8-7.7
	Tuberculosis	9.7	4.0-5.2
Eosinophils	Healthy	0.3	0.2-0.5
	Tuberculosis	0.2	1.7-3.8
Lymphocytes	Healthy	2.0-8.0	1.0-5.2
	Tuberculosis	4.7	1.5-2.1

* 0-5 years of age. ** > 11 years of age.

Table 5: Biomarkers for immunodiagnosis of tuberculosis in children and adults.[25,47,49-68]

Biomarker	Neonatals-infants	Adolescents and adults
Extracellular vesicles (EV)	Blood: LAM and LprG have been detected by immunoassay	Urine: LAM and CFP-10 (Rv3874) have been detected by I-PCR Serum: *M. tuberculosis* peptides by MRM-MS
Cytokines	Sputum: IFN-γ and IL-2 detection by ELISPOT Blood: detection of IFN-γ, IP-10, (TNF)-α, IL-1ra, IL-2, IL-13 and MIP-1β by multiplex immunoassay	Blood: Detection of IL-2 IL-1ra, IL-10 and TNF-α by multiplex immunoassay
miRNAs	Blood: the combined identification of: miR-1, miR-155, miR-31, miR-146a, miR-10a, miR-125, miR-150, miR-29 up regulated with 95.8% sensitivity and miR-29 down regulated with 95% sensitivity Serum: detection of let-7e, miR-146a, miR-148a, miR-192, miR-193a-5p, miR-451, miR-532-5p, miR-590 -5p, miR-660, miR-885-5p, miR-223, miR-30e, miR-25, miR-146	Pleural fluid: the combined identification of miR-3615, miR-4616, miR-378i that are expressed upwards in patients with active and latent TB Serum: A promising biomarker for the diagnosis of MDR-TB is Let-7e-5p, miR-155, miR-21-5p, miR-92a-3p and miR-148b-3p, miR-21-5p, miR-92a-3p and miR-148b-3p Sputum: miR-151, miR-409-3p, miR-1204, hsa-miR-376c, miR-23a Serum/Sputum: miR-1270, miR-371-3p, miR-380, miR-582-3p, miR-618
IP10/CXCL10	Blood: Detection of IP-10 using a sandwich ELISA	Urine: detection of IP-10 associated with treatment efficacy by ELISA
Lipoproteins	Plasma: *M. tuberculosis* lipoprotein (TLP) by ELISA	Serum: lipoprotein capture assay by ELISA
75 metabolites	Serum: detection of metabolites (leucine and kynurenine) by mass spectrometry	Urine: N-acetylhexosamine, neopterin, diacetylspermine and sialic acids by mass spectrometry

ELISPOT = enzyme-linked immunosorbent spot. I-PCR = immuno-polymerase chain reaction. MRM-MS = multiple reaction monitoring mass spectrometry assays. Bioplex = multiplex immunoassay. ELISA = enzyme-linked immunosorbent assay.

From these findings, new tools have been developed such as immunoprofiles or immunological profiles, miRNAs, measurement of soluble metabolites (such as cytokines, chemokines or growth factors) and the use of new tools such as transcriptomics and multiomics that improve the diagnosis of TB based on biomarkers present in accessible samples such as peripheral blood, saliva or urine *(Table 5)*.[47,49-65] The use of miRNAs in adults has proven to be effective in discerning between PTB and other types of pathologies (lung cancer and pneumonia).[25] Regarding other methods such as the use of biomarker cytokines, it has demonstrated potential in the detection of PTB in children with high levels of sensitivity and specificity.[66] Although these TB biomarkers are still in the experimental and preclinical stage, few progress to a validation stage,[67] so they are only alternatives for the

detection of *M. tuberculosis* and seek to solve the problems represented in diagnosing.

Timely and accurate diagnosis of PTB is a determining factor for early detection and essential for achieving compliance with global TB control programs.[16] That is why it is important to validate new biomarker-based TB diagnostic methods.[65,67,68] Unfortunately, few biomarkers progress to a developmental stage, so validation and application design studies for the use of biomarkers in PTB diagnosis and drug treatment monitoring are required to be funded. So far, only the measurement of biomarkers has been used as alternatives for the detection of *M. tuberculosis* in difficult to diagnose patients, such as the diagnosis of PBT in children.

CONCLUSIONS

Diagnosis of TB in children and adults requires a high index of suspicion, a thorough assessment of clinical and radiological features, and judicious use of diagnostic tests. Although the clinical and immunological characteristics of TB are similar in both populations, there are differences that must be taken into account when making the diagnosis. Further research is required to develop more accurate and reliable TB diagnostic tests, especially in children.

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