Case Report **Open Access**

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How to manage TB in children? Problems and solutions in four cases

Abstract: Children bear a substantial part of the tuberculosis (TB) epidemic worldwide, and it is estimated that there were ≅ 500.000 childhood TB cases globally in 2010, although accurate data are problematic to obtain given the many difficulties associated with TB diagnosis in children and the weaknesses of surveillance systems in countries where TB is endemic. The World Health Organization is working hard in order to reduce the TB prevalence rates and deaths by half by 2015. In this challenge, general practitioners and pediatricians play a key role in detecting early cases of suspected TB and sending them to experts in infectious diseases. This will reduce delayed diagnosis and the spread of disease, which is especially important now that the prevalence of multidrug resistant TB is increasing. For this reason, the purpose of this report was to delineate the characteristic clinical features of the most common forms of pediatric TB and to suggest a rational and practical approach to the disease underlining the role of patients and parents personal and clinical history.

Keywords: Tuberculosis, Children, Case-report, Management, Therapy

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1 Introduction

Tuberculosis (TB) is an airborne infectious disease caused by bacteria of the *Mycobacterium tuberculosis complex*. Even if it represents a preventable and curable disease, TB is still a major cause of morbidity and death worldwide.

Recently, the World Health Organization estimated 8.8 million incident cases of tuberculosis (TB) globally in 2010: 1.1 million deaths among HIV-negative subjects and an additional 0.35 million deaths among HIV-positive subjects.1 About 1 million TB cases involve children (75% of them occurring in 22 high-burden countries), with a global estimate of 130,000 deaths per year, making TB among the top 10 causes of death in childhood. Regional data from the World Health Organization in 2007 showed that smear-positive TB in children <14 years of age accounted for 0.6–3.6% of reported cases [1].

Infection rates are highest in Africa, Asia, and Latin America while, in industrialized countries, most cases occur in foreign-born populations.

Nowadays, in fact, TB is an emerging disease also in developed countries, probably due to a new migration flow of a variety of populations.

The present paper aims to analyze a series of "TB sample cases" observed during a four months period in order to focus on this progressively more common disease and review its management.

2 Case 1

A two years old girl was admitted to our division because of fever, cough and dyspnea. The girl had arrived in Italy from Romania just seven days before when she reached his family living in a nomad camp. The first chest x-ray showed right pleural effusion and right middle and lower lobes consolidation. Antibiotic therapy was started without any clinical benefit. Therefore, a tuberculin skin test (TST) was

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performed with a markedly positive result after 72 hours. Because of sudden worsening dyspnea, emergency chest computed tomography (CT) was carried out and the presence of relevant pleural effusion all around the right lung, with parenchymal lung consolidation and paratracheal, subcarinal and hilar lymphadenopathy was highlighted (Figure 1). Interferon-γ releasing assay (IGRA) tests firstly gave an indeterminate result but, repeated a week later, it gave a positive result. An evacuative thoracentesis was made and polymerase-chain-reaction (PCR) resulted positive for *Mycobacterium tuberculosis* (Mtb). An anti-TB therapy with isoniazid (INH), rifampicin (RMP) and pyrazinamide (PZD) was begun with rapid improvement of the girl's clinical conditions. All the microscopic, nucleic acid amplification techniques and cultural exams carried out on gastric lavages and urine gave negative results for Mtb. The last chest x-ray, carried out after one month of therapy, showed an almost complete resolution of the pleural effusion, of the parenchymal disventilation areas and of the lymphadenopathy.

2.1 Case 1: discussion

About 75% of childhood TB disease is pulmonary [2] and up to a third of all pediatric pulmonary TB cases may be complicated by pleural effusion, which may also be found without any significant concomitant parenchymal disease [3]. Pulmonary TB commonly presents with a persistent (>21 days) and unremitting cough, with or without fever, not improving despite appropriate first line antibiotic treatment.

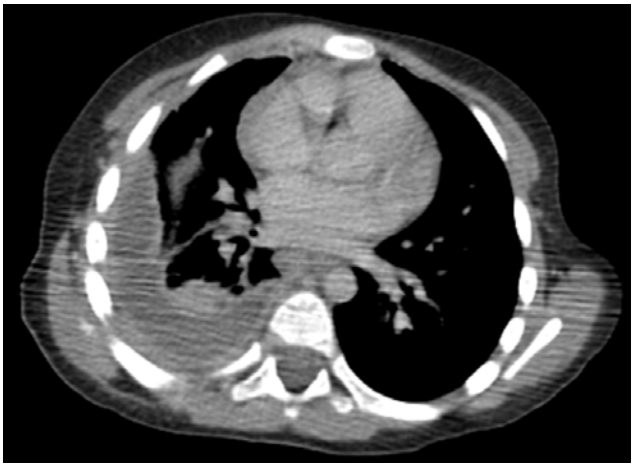

Figure 1: Chest computed tomography revealed the presence of relevant pleural effusion all around the right lung, with parenchymal lung consolidation and paratracheal, subcranial and hilar lymphadenopathy.

The diagnosis of TB is not usually considered in a febrile child unless the fever is persistent (> 7 days) or other clinical features suggestive of TB are present. Positive family history for travelling or origins from TB endemic countries and overcrowded living environments should induce the diagnostic suspicion of TB.

The examination of pleural fluid is important to establish the diagnosis of TB pleuropneumonia. Nevertheless, cultures of the fluid are positive only in a low number of cases and it takes them a long time to get the result. Nowadays PCR is an helpful diagnostic tool for early diagnosis and it has good sensitivity and specificity.

During the last years, IGRA was introduced into clinical practice as a diagnostic tool with high specificity for the diagnosis of Mtb infection, even though it is not able (as TST) to discriminate between active TB disease and latent TB infection. During childhood, due to the lymphocytic anergy secondary to infections, IGRA tests may initially give indeterminate results. As a consequence, in case of strong suspicion of TB, IGRA should be repeated even in case of undeterminate results.

3 Case 2

A five year old girl, born in Romania and affected by neonatal hypoxic-ischemic encephalopathy, was admitted to our division because of fever and lymphadenopathy. The lymph-node was a latero-cervical, unilateral, painful, swelling lymph node fixed but soft in the middle, with the overlying skin appearing thin, shiny and erythematous. Lymph node characteristics did not change despite amoxicillin -clavulanate and anti-inflammatory therapy.

The neck ultrasonography (US) highlighted hypoecoic, bunched, necrotic lymph nodes measuring 4.5 cm as a whole.

TST showed a positive reaction (>15 mm induration) and the IGRA was positive.

Ziehl Nielsen staining of the smears, cultures and nucleic acid amplification, collected by three early morning gastric washings and performed for up to three consecutive days, gave negative results for Mtb. Urine tests (Ziehl Neelsen staining, cultures and nucleic acid amplification) were negative too. Chest x-ray and abdominal US evaluation were negative.

Surgical evaluation was performed and lymph nodes drainage was carried out by fine needle aspiration. The analyses carried out on the drained material showed a positivity of nucleic acid amplification (PCR) for Mtb.

An anti-TB therapy with INH, RMP and PZD was begun. After the beginning of the therapy, girl's clinical conditions improved, fever disappeared and lymph nodes size progressively diminished.

3.1 Case 2: discussion

TB lymphadenitis in superficial nodes is the most common form of extrapulmonary TB in children. The laterocervical nodes become involved secondary to the extension of a primary pulmonary lesion. Lymph nodes localization develops 6-9 months after an initial TB infection.

In developed countries more than two-thirds of pediatric lymphadenopathy have infectious causes other than TB, therefore cases of lymphadenitis are commonly treated with a high-spectrum antibiotic; nevertheless, it would be mandatory to give the instruction to return for reevaluation in case of no clinical improvement in order to perform other investigations to reach a final diagnosis.

In our case, patient's medical history, familiar origins from a TB endemic country, and the particular lymph node characteristics (unilateral, involving multiple nodes, fixed to underlying tissues, initially non-tender, solid, covered by erythematous skin and successively tending to colliquation and fluctuation), should give the suspect of TB etiology and allow the beginning of the diagnostic procedures described in our clinical case. Systemic signs and symptoms other than low grade fever are usually absent.

Primary medical treatment, aimed to reduction of the high-grade inflammation, could be also followed by surgical removal in order to prevent fistulae development [4].

Since cross-reactivity between PPD-Mantoux test and non tubercular micobacteria (NTM) antigens, and less likely between IGRA tests and NTM antigens exists, microbiological tests performed on the infected lymph nodes should be the basis of differentiating between NTM and tuberculous lymphadenopathy [5,6].

4 Case 3

A two years old child of Rumanian origins, born in Italy to a TB-affected mother, was admitted to our division because of persistent fever (39°C). Chest radiography revealed a typical miliary reticulo-nodular pattern (Figure 2).

IGRA tests, as well as Ziehl Neelsen staining of the smears, cultures and nucleic acid amplification (collected by undertaking three early morning gastric aspirate for up to three consecutives days), gave positive results for Mtb. Anti-TB therapy with INH, RMP, PZD and Etambutol (ETM) was begun.

Nevertheless, only few hours after the beginning of therapy, the patient presented drowsiness and a diminished level of consciousness, horizontal nystagmus, trismus, frontal release signs (suck), miosis with loss of reaction to light. Cerebrospinal fluid examination was performed and revealed the presence of Mtb nucleic acid. A non-contrast head CT scan showed two hypodense space-occupying lesions in the subcortical white matter and in the knee of the right internal capsule.

TB meningitis was therefore diagnosed and corticosteroid therapy was begun with a rapid improvement of his clinical conditions. However, a left hemiparesis appeared. Contrast-enhanced brain magnetic resonance imaging (MRI), performed one week after, showed meningeal enhancement, a reduced measures of the space-occupying lesion in the subcortical white matter, abnormal enhancement of basal cisterns and decreased diameter of the focalised lesion of the right internal capsule knee (Figure 3). A few weeks later, the child presented vomiting, apathy and drowsiness. The non-contrast head CT scan highlighted the presence of obstructive hydrocephalus and signs of intracranial hypertension (enlarged ventricles and peri-ventricular hypodensities).

The child underwent ventricular-peritoneal derivation and symptoms resolution was achieved.

The last contrast-enhanced MRI showed enlarged ventricles with no signs of intracranial hypertension and the presence of a focal lesion at the knee of the right internal capsule. An angio-RMI study showed no vascular abnormalities. To date, the patient shows good clinical conditions, although the left hemiparesis, requiring long term physiotherapy, is still present.

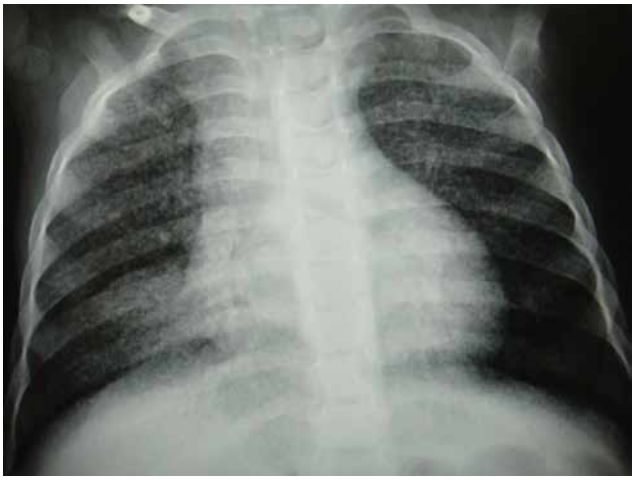

Figure 2: Chest radiography revealed a typical miliary reticulo-nodular pattern

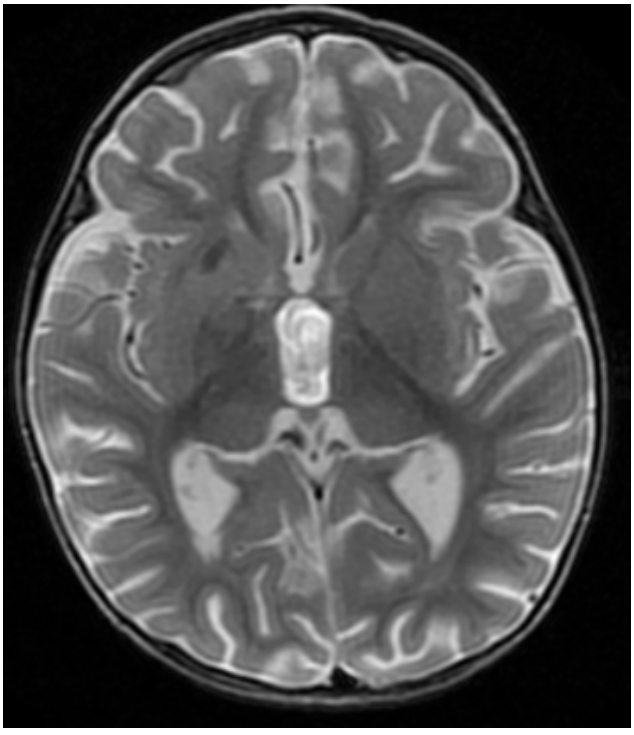

Figure 3: Contrast-enhanced brain magnetic resonance imaging showed meningeal enhancement, a reduced measures of the space-occupying lesion in the subcortical white matter, abnormal enhancement of basal cisterns and decreased diameter of the focalised lesion of the right internal capsule knee.

4.1 Case 3: discussion

An erosion of a parenchymal focus of TB into a blood or lymphatic vessel may result in dissemination of the bacilli and in a miliary pattern, with small nodules on the chest x-ray. The TB meningitis is the most severe extra-pulmonary TB-related complication [7], that results from hematogenous spread of primary or postprimary pulmonary disease or from the rupture of a subependymal tubercle into the subarachnoid space in a time of 3-6 months generally. A lot of cases show old pulmonary lesions or miliary pattern on chest radiograph. In fact, it's accepted a close concordance between TB meningitis and miliary TB in young children.

Because of the haematogenous spread of bacilli during a lung miliary pattern, it is important to considerate the possibility of an extra-pulmonary involvement.

In clinical practice two different types of Central Nervous System involvement may develop: tuberculoma and meningitis.

Tuberculoma usually shows a good response to treatment, with resolution of acute signs and symptoms, even if with the possibility of sequelae depending on the first focal lesion. In contrast, the treatment of a meningeal involvement is still a clinical challenge. In fact, in our case, the anti-tubercular therapy was effective against lung and brain lesions, but the meningeal involvement showed a progression, up to meningeal thickening and hydrocephalus.

The accelerating clinical illness usually correlates with the development of hydrocephalus, as in the present case. Even the use of high-dose corticosteroids may not stop meningeal inflammation. However, clinical trials demonstrated that corticosteroids should be routinely used in HIV-negative patients with TB meningitis to reduce death and disabling residual neurological deficits among survivors [8,9], although sometimes more aggressive anti-inflammatory drugs may be needed [10]. Sometimes profound abnormalities in electrolyte metabolism may be observed, due to salt wasting syndrome or development of syndrome of inappropriate antidiuretic hormone secretion. We concluded the management of our patient with an angio-RMI study. TB can be considered as a vasculitis, and a significant percentage of children with TB generally presents ischemic brainstem lesions. Moreover, studies are necessary to show the exact meaning of these lesions, their implication for the patient's management and the possible use of anti-inflammatory and of anti-platelets agents to prevent neurological lesions and sequelae [11].

5 Case 4

The present case deals with a premature female infant, born in Italy from a Nigerian mother with HIV infection and pulmonary TB during pregnancy. The infant came to our attention, after having been in another hospital, because of pulmonary TB and HIV infection.

At birth, she had an episode of asphyxia and was transferred to a Neonatal Intensive Care Unit (NICU). Two months after discharge from NICU, the child presented with weight loss, diarrhea, dehydration and acute severe dyspnea. Admitted to the Pediatric Intensive Care Unit, she was intubated and ventilated. Here the diagnosis of congenital HIV and TB was achieved on the bases of positive bacterioscopic analysis and PCR on the bronchoalveolar lavage, positive IGRA, positive bacterioscopic and cultures analysis on urine, positive cultures on the gastric aspirates and the presence of typical lesions in pulmonary CT scan. Abdominal US revealed two hypoechoic hepatic lesions and a hypoechoic spleen area. A case of congenital TB was then suspected because of urine positivity for Mtb and both liver and spleen hypoecoic lesions.

She was admitted to our division in order to continue the anti-TB (INH, PZD, and ETM), corticosteroid and

highly-active anti-retroviral therapy (HAART). An antibiotic prophylaxis with cotrimoxazole was also begun.

The 6 months follow up shows a child in good clinical conditions.

5.1 Case 4: discussion

Congenital TB is a rare manifestation of TB [13,14].

Clinical manifestations of congenital and neonatal TB are non-specific, they usually present like neonatal sepsis and diagnosis is often delayed [15-18]. Low birth weight and prematurity are common features of HIV and TB infected neonates born to HIV-infected mothers with TB [19].

Cantwell et al proposed diagnostic criteria for congenital TB. Among them we mention the onset of TB clinical manifestations in the first two weeks of life, the presence of a primary focus or granulomas in the liver and the demonstration of placenta and genital area contamination. These criteria increase diagnostic sensitivity, but the diagnosis remains difficult since confirmation of the primary complex or detection of granulomas in the liver has to be carried out by biopsy, which is not always available [20]. In our case a liver biopsy was never performed [15].

The co-infection between TBC and HIV really represents a clinical challenge for physicians, especially in childhood. Impressively, HIV-infected children demonstrate an increased risk of rapid disease progression, unsatisfactory treatment response and TB recurrence; moreover, TB mortality is six times higher among HIV-infected children than among uninfected ones [21]. It has been showed that a close link exists between clinical developments of these two infectious diseases. On one hand TB is able to induce a quicker progression of HIV disease by increasing viral replication and reducing CD4+ T-cells counts. On the other hand, since protective immunity to TB infection depends on the CD4+ T-cell subset [22], HIV infected children with decreased CD4+ T-cells count are at greater risk of TB disease progression [23].

TB treatment of HIV-infected children is a challenge, too. The lack of clinical trials in children creates concerns regarding common toxicities, drug interactions, side effects and the best time for the introduction of HAART following TB diagnosis. In fact, the management of TB in HIV-infected children usually deviates from standard protocols. Despite local and international guidelines, therapy often has to be individualized.

Regarding the best time to introduce HAART, WHO recommends to begin the treatment at different time points, starting earlier in the more immunocompromised children or where response to TB treatment is poor [24, 25].

The management of TB-HIV co-infected children is of special difficulty due to the peculiar immunologic background and the extensive drug-drug interaction, and so requires a broader and specific discussion, which is above the purpose of this manuscript.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Informed consent: Informed consent has been obtained from all individuals included in this study.

6 Conclusions

The global burden of TB continues to grow due to several factors, such as population migration patterns, crowded living conditions in developing countries and the impact of HIV epidemics, that is driving the rise of TB in countries with high prevalence of HIV. We described four "teaching" TB cases that came to our attention almost contemporary in a very short period (only four months). We choose these cases because they are instructive and paradigmatic for TB disease.

TB management in childhood still represents a challenge for pediatricians. Currently the available diagnostic tools include immunologic, microbiological and radiological assays. These assays are Tuberculin Skin Test, IFN-y releasing assays (IGRAs tests), radiologic findings, microscopic examination of acid-fast-stained smears, traditional culture, which remains the gold standard in TB diagnosis, and nucleic acid amplification techniques. However, preliminary data suggest that high resolution computed tomography and new quantiferon tests adapted to measure also EGF, sCD40L, VEGF, MIP-1beta, TGF-alfa and interleukin-1alfa will help physician for early diagnosis of active disease [26]. Nevertheless, anamnesis should already induce the clinical suspicion. As demonstrated in our case series, each child came from endemic countries (the 1th, 2th and 3th from Romania and the 4th from Nigeria), had migrant parents (cases 1,3,4) or lived in crowded environmental conditions suggesting a higher risk of TB infection (the patient in the 2th case lived in an orphanage).

Due to the low probability of transmission between very young children, screening of other children is usually largely unproductive. Therefore, when a TB process/infection is detected in children, it's important to demonstrate whether the source of Mycobacteria is in parents or in other cohabitants, such as in the cases 3 and 4, or in school contacts. Nevertheless, TB transmission in a non-household setting is difficult to detect, because contact with the source case is often not obvious, even if described in some case reports [27].

A particular attention must be paid to signs and symptoms referred by parents about their clinical conditions: for example, the 3th patient's mother has always denied having fever and cough, but pressing her, we concluded she's affected by contagious pulmonary TB. These case series should be a reminder to health professionals about the importance of a careful investigation around a case of pediatric TB, in order to prevent further disease transmission.

Besides, in presence of suggestive symptoms/signs of TB infection, first line tests such as TST, IGRA and/or chest x-ray may help in the diagnostic process. In case of positive results, secondary diagnostic tools (microscopic examination of acid-fast-stained smears, traditional cultures of biological fluids, nucleic acid amplification, CT, MRI) are needed to confirm diagnosis [28].

Concerning TB therapy, the optimal treatment is still discussed, especially in children. In general, the treatment of clinical TB consists of a 2-month initial phase of INH, RMP and PZD followed by INH and RMP administration for 4 months. A longer continuation phase and the addiction of further drugs are necessary in HIV-infected children, TB meningitis and complicated extrapulmonary TB or when drug resistance is suspected to be high.

One hundred twenty-eight years after the Koch's discovery of Mt, the disease remains a threat and an important cause of death worldwide. Prevention, early detection and diagnosis, and medication adherence are key tools in order to eradicate this killer disease. Healthcare providers must play an important role in this regard.

Conflict of interest statement: Authors state no conflict of interest

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