SEVERE CASES OF PEDIATRIC TUBERCULOSIS

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Abstract

Pediatric tuberculosis (TB) represent a warning sign in a community, as it could signal recent TB infection of a contagious form in an adult. Rapid diagnosis is very important for effective treatment in children, and it is mandatory for the efficient control of tuberculosis at the public health level, since it allows rapid identification of contagious adult cases. Here we report three severe cases of TB in children, one of them occurred in a HIV positive patient. These cases stress the need for an extensive medical history, a complete clinical and physical examination of the patient and radiological examination during diagnostic work-up. This includes: the positive history for contact with infected adults; the presence of risk factors; the evaluation of the immunological status; exclusion of TB diagnosis for persistent respiratory symptoms (2-3 weeks) after antibiotic therapy; the presence of radiographic abnormalities and the detection and isolation of the Mycobacterium Tuberculosis in the appropriate specimens for bacteriological examination. Early diagnosis and treatment are extremely important once tuberculosis is suspected, to improve survival and prevent morbidity.

Key words: pediatric tuberculosis, miliary, HIV infection, diabetes mellitus

Introduction

Tuberculosis (TB) is still a major public health problem worldwide. According to the latest estimation of the World Health Organization in 2014, 9.6 million new cases were reported and 1.5 million new death cases. Approximately 1.000.000 new cases of TB in children occur in children less than 15 years [1]. This high level of incidence of TB in children is probably underestimated due to the frequent involvement of individuals with poor social-economic status, that have no access to investigation and treatment, but also due to diagnostic difficulties by non-specific symptoms and bacteriological confirmation. [2,3]. Romania ranks first in the EU in the level of TB incidence, with 81/100.000 population new cases and 639 (4%) cases aged under 15 years, although there is a downward trend in the past few years [1,4]. A high level of TB epidemic is associated with an elevated incidence of infection in the general population, children being a vulnerable population. Studies show that approximately 50% of infected children are at risk to develop active disease in the absence of prophylactic treatment [5,6]. This risk is increased in the presence of favorable conditions such as immunosuppressive diseases (HIV, diabetes), hypotrophy and poor socio-economic conditions [7]. We report 3 cases with severe forms of TB in children; one with miliary, one with extensive cavitary TB, highly contagious and the last one with meningitis tuberculosis in a positive HIV patient. These cases had diagnostic, evolution and therapy particularities, all having a high degree of severity by lesion extension and the association of other pathologies that have increased the difficult therapeutic approach.

Case report 1

We present a case report of a male patient, aged 4 years, in the care of grandparents, with poor housing. The patient was admitted to the Pediatric Pulmonology Department with malaise, fever, sweating, vomiting, headache, dysphagia, anorexia, weight loss, productive cough and dyspnea at small efforts. The symptoms had an insidious onset, a month before admission, with a worsened progress. Objective - hypotrophy (BMI – 11.1 kg/m^2), pale, lips cyanosis, tachypnea. Pulmonary: vesicular murmur present, no crackles, SpO_2 88%, BP 80/50 mmHg, HR 120/min. Tuberculin skin test (TST) 5U negative PPD. Biological: ESR 51mm/h, WBC 10.000/µL, Hb 10g/dl, PLT 710.000/µL, TGO/TGP 118/58. Chest radiography (Figure 1) revealed multiple micro-nodular opacities, unorganized, pale, vague outlined, disseminated in both lung fields, with a suggestive aspect of miliary TB. Because the suspicion of meningitis has been raised, lumbar puncture was performed. Cerebrospinal fluid examination revealed negative Pandy`s reaction, element 75/mm^3, 15% nutrophils, 85% lymphocytes, acid-resistant bacilli in microscopy and culture negative. GeneXpert of gastric lavage test was negative for Mycobacterium tuberculosis. Etiology of TB sputum examination by culture on solid medium confirmed positive for BK. Negative HIV test. The final diagnosis was: Miliary tuberculosis; Acute respiratory failure; Hepatic cytoloysis.

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Patient followed anti-tuberculosis treatment regimen according to the National Guidelines for Prevention, Surveillance and Control of Tuberculosis with Isoniazid (HIN) 65 mg, Rifampicin (RMP) 150 mg, Pyrazinamid (PZM) 325 mg, Ethambutol (EMB) 200 mg, Hemisuccinate hydrocortisone 200/day (for a week), afterwards corticosteroid therapy with oral Prednisone 20 mg/day with progressive decrease within 4 weeks, gastric and hepatic protectors, Mannitol 20%, 500ml/day, oxygen, vital functions monitoring. Evolution was shifting with multiple episodes of acute respiratory failures and febrile exacerbations in the first two weeks of treatment, and then progressively, patient condition improved significantly.

Case report 2

Female patient aged 15 years, student in the IX class, know with type I diabetes mellitus, insulin required for over 3 years, treated with Novorapid 12 U 3 times/day and Lantus 22U at 10 pm, is hospitalized in the Pediatric Pulmonology Department for muco-purulent coughing, with insidious onset for over two months. Physical examination reveals an overweight patient, BMI- 27.5 kg/m2, paleness. Pulmonary – respiratory murmur present, no crackles, SpO2 99%, HR 120/min, BP 100/50mmHg. Biologically were observed mild anemia, severe inflammatory syndrome (Hg 11.3 g/dl, MCV 75.7 fL, MCH 23.3 pg, MCHC 30.7 g/dl, WBC 8500/µL, normal leukocity formula, Thrombocytes 373.000/µL, ESR 81 mm/h), blood glucose 383 mg/dL, urinalysis glucose >500 mg/dl, otherwise normal. Chest radiography (Figure 2) highlights stretched opacity, unorganized, comprising the upper half of the left hemi-thorax, pale, heterogeneous by the presence of multiple hyper-transparent images inside, of various sizes, suggestive for left extended cavitary pulmonary secondary tuberculosis. The case was confirmed, being positive in microscopy for acid-resistant-bacilli (+++) and rapid culture (BACTEC). Specific anti-tuberculosis therapy was initiated with a 4 drugs scheme, diet with 200 mg hydrocarbons/day, insulin therapy and hydration. Product tolerance was good, symptoms remitted after three weeks.

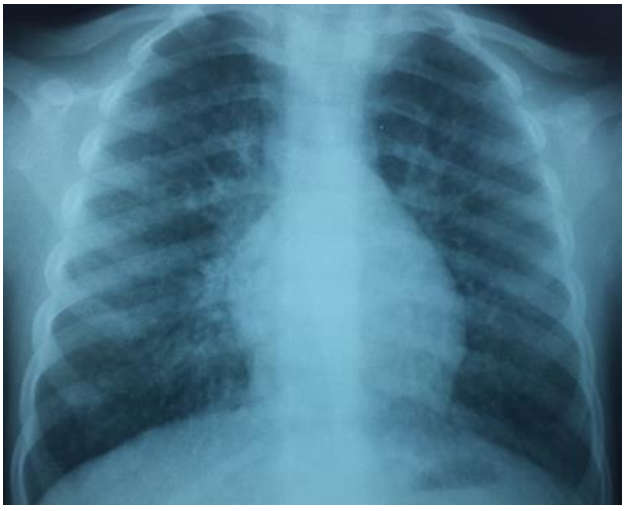

Figure 1. Chest radiograph case 1, miliary TB.

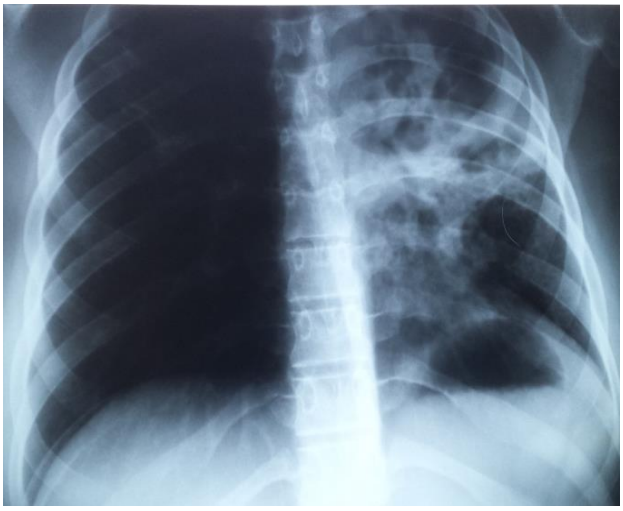

Figure 2. Chest radiograph case 2, cavitary TB.

Case report 3

We present the case of a male patient, aged 17 years, who comes in the Department of Infectious Diseases with high fever (39C), headache, chills, photophobia, neck stiffness, drowsiness, vomiting. These symptoms started insidious, 10 days before admission with progressive evolution towards aggravation into a coma in the first 12 hours of hospitalization. The patient was known to have HIV from the age of 3 years, with antiretroviral therapy instituted at the age of 10 years, with noncompliant therapy, reflected in the evolution of viral load and CD4 values (Table 1, Figure 3). Physical examination revealed severe general condition, initially conscious, collaborator, drowsiness, subsequently loss of consciousness, superficial coma (grade I). Spinal puncture revealed cloudy cerebrospinal fluid, biochemical and cytological features where suggestive for TB etiology, confirmed by positive rapid culture (BACTEC). The treatment was specific anti-tuberculosis regimen I with Isonizid 10 mg/kg/day, Rifampicin 15 mg/kg/day, Pyrazinamide 30 mg/kg/day administered rectal in suppository form and Streptomycin 15 mg/kg/day intra-muscularly. Favorable clinical evolution is slow, patient coming out of coma after 21 days. After two months intense fever and headache reappear and CSF examination reveals the presence of Cryptoccocus neoformans. Treatment was associated with Amphotericin B in dose of 0.5-0.7 mg/kg/day, for five days and afterwards Fluconazole 400 mg/day for five days, then 200 mg/day for 10 days, being discharged after 3 months of hospitalization with good general clinical condition. Discharge recommendation was to continue tuberculosis therapy under direct observation (DOTS) at home. After another 3 months of treatment, the patient returns with malaise, fever, chills, headache, nausea, legs numbness and multiple peripheral lymphadenopathy. Physical examination reveals pale skin, sinus sensitive points, with no signs of meningeal irritation.

Biologically was noted ESR 30 mm/h, fibrinogen 638 mg/dl, Hg 8.5g/dl, SGOT/SGPT 150/120. In the cerebrospinal fluid examination, genetic testing for Mycobacterium tuberculosis present BAC revealed resistant to rifampicin. Anti-tuberculosis regimen was reconsidered by associating Ofloxacin 800 mg/day, Ethambutol 1200 mg/day. Antibiotic treatment with large spectrum was associated (Ceftriaxonum 2g/day, Gentamicin 160mg/day, antimicotic (Fluconazole 400mg/day), Mannitol 20% 500ml/day, corticosteroids (Hemisuccinate hydrocortisone 200 mg/day iv). The dynamic evolution was unfavorable, with general condition gradually deteriorating, paraparesis, convulsions and seizures, loss of consciousness, coma and death in a month of hospitalization.

Table 1. Evolution of viral load between 2002-2012, case 3, TB meningitis.

Year	2002	2003	2005	2006	2008	2009	2010	2011	2012
Viral load (copies/ml)	22000	<400	<400	2720	52500	122000	116000	316	38000

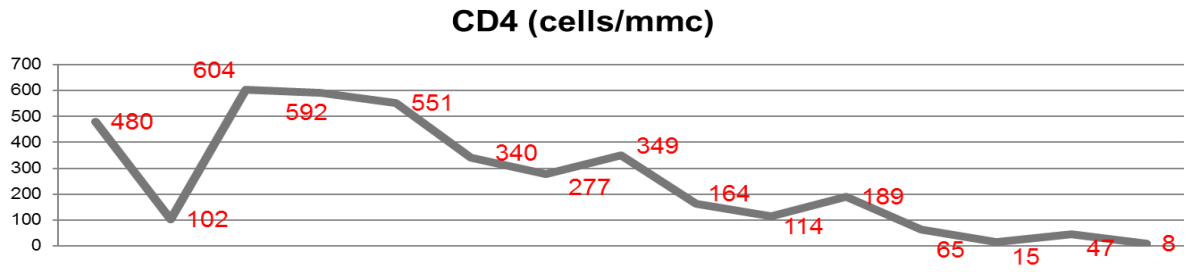

Figure 3. Variation of CD4 lymphocytes between 2002-2012, case 3, TB meningitis.

We report 3 cases, severe forms of TB in children, a case of miliary, a case of extensive cavitary TB, highly contagious and a case of meningitis tuberculosis in a patient HIV positive. The diagnosis of tuberculosis in children is a very difficult one, given that clinical presentation is often non-specific and bacteriological confirmation is obtained in less than 15% of the cases [7]. This is the main reason for a detailed assessment of all the evidence derived from a careful history of exposure, clinical examination and relevant investigations. To formulate a positive diagnosis of TB in children, the following criteria must be considered: careful history (including history of TB contact and symptoms consistent with TB); clinical examination (including growth assessment); tuberculin skin testing; chest radiography (if available); bacteriological confirmation whenever possible; investigations relevant for suspected pulmonary Tb and suspected extra-pulmonary TB [8].

In the first case we reported a miliary TB diagnosed at a very young age, only 4 years old. Risk factors in this case were hypotrophy weight and poor socioeconomic conditions. Malnutrition is associated with impaired call-mediated immunity, favoring rapid progression of TB infection to severe disease, disseminated, and threatening, as miliary asphyxia[8,9]. Moreover, living in small enclosed residences with poor ventilation increases the risk of infections in the presence of contagious TB cases [9]. Ignoring non-specific symptoms by people who care for children, their lack of health education, are also factors that can result in delayed diagnosis and disease progression to sever forms: miliary, meningitis, TB bronchopneumonia. Miliary TB is a hematogenous dissemination form of bacilli tuberculosis, child specific. It`s starting point is one of the primary component complex (lymphadenopathy caseous) and can occur in the first weeks after the initial infection [10,11]. Miliary TB is a particularly severe, disseminated disease, which can involve the lungs, meninges and/or other organs (liver, spleen, lymph nodules). In this case, to assess the implication of other organs beside the lungs, biological test was performed for the hepatic function and lumbar puncture with cerebrospinal fluid analysis. These findings have sustained the liver damage in the absence of the meninges impairment. Repeated episodes of acute respiratory failure presented by this patient can be explained by the density of the millar miconodules and by the exudative alveolar peri-micronodular reaction with inflammatory hyperergic condition. For this reason, anti-inflammatory medication, corticosteroid type, was added, which along with anti-tuberculosis therapy led to a favorable outcome.

Cavitary forms of TB, such as case 2, are usually found in adults, and their occurrence in children is a warning to the community [12]. Late discovery of a case of extended pulmonary TB, highly contagious, into a community of children, raises major epidemiological problems through both receptive hosts and the extent of epidemiological investigations. Intensive detection is to identify suspects by primary care services, school doctors, and community care network [13]. Usually child tuberculosis is a non-contagious form, but in immune-compromised cases, infection can lead to primo-secondary forms, severe, diseminated and highly contagious; cavitary lesions have between 10 million – 1 billion bacilli compared to nodular lesions that have

between 100-10000 bacilli [9]. Diabetes is a risk factor that should be an argument for careful monitoring with regular clinical checks, regardless of age [14]. The relative risk for TB among diabetic patients ranges between 2.44 - 8.33 compared to the general population [15]. Studies have shown that in patients with diabetes, anti-infective defense mechanisms are altered by reduced macrophages alveolar activation and reduced amount of interferon gamma produced by CD4 [16]. In the presented case, pulmonary tuberculosis appeared on the background of uncontrolled diabetes type 1. Insidious symptoms led to a late detection of TB, with important pulmonary parenchyma lesions through multiple cavities, extended in the left lung. The prognosis of this case is reserved, burdened by the risk of major sequelae healing with left fibrotorax, negative cavity syndromes, chronic respiratory failure, massive hemoptysis, pulmonary aspergillosis or lung suppurations. Careful monitoring of the therapeutic regimen is recommended, patient having indications for extended therapy for 8 months to 1 year, considering the pharmacological particularities given by the presence of diabetes [17]. Low concentrations of rifampicin, the changes in absorption, low protein binding medication are factors of bad therapeutic response with risk of failure and possible resistance to anti-tuberculosis therapy [18,19].

In patients with HIV, the occurrence of TB meningitis is closely related to the severity of immune depression, CD4 lymphocytes being significantly decreased. People with HIV have a 20-30 times higher risk of TB compared to healthy individuals [19]. In general, tuberculosis is the most common pathology associated with HIV infection in high endemic territories, such as in this case [20], and central nervous system TB is the most severe form of TB in this population, with a mortality up to 67% compared to 25% in immune-competent individuals [21]. Prognosis depends on the speed of diagnosis and treatment initiation [19,22]. It requires rapid exclusion of other forms of meningitis with other opportunistic pathogens (Cryptococus neoformans, Toxoplasma gondii). In our case the diagnosis was confirmed by positive bacteriological culture in liquid medium (BACTEC) within 10 days, but therapy was initiated from the first day, based on clinical suspicion and biochemical changes in the cerebro-spinal fluid. Currently, genetic tests of DNA amplification Mycobacterium (GeneXpert, LPA) may have an important role in rapid diagnosis (2 hours) of TB meningitis and resistance to Rifampicin. However, the diagnosis cannot be excluded on the basis of a negative result, sensitivity being between 50-60% [23]. In the reported case, the unfavorable evolution concluded with death can be explained, on one hand, by the existence of two diseases that negatively influence each other, and on the other hand, by the non-compliant treatment. The fact that the patient returned after three months from the first hospitalization with engraved general condition and rapid genetic testing for BK showing a resistant germ to Rifampicin, highlights the difficult therapy given by the association of the two pathologies, high risk selection of resistant germs population, increased complication risk, emphasized also by the non-compliance to therapy.

Conclusions

Tuberculosis in children raises diagnostic, treatment and monitoring problems. Early diagnosis and treatment are extremely important once tuberculosis is suspected, to improve survival and prevent morbidity. The multidisciplinary approach to these cases can lead to therapeutic success, especially for severe forms of TB.

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