

CASE REPORT

EXTRA PULMONARY TUBERCULOSIS IN CHILDREN

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SUMMARY

Background: Tuberculosis is a highly contagious disease, produced by *Mycobacterium tuberculosis* (Koch bacillus). The evolution of this disease is chronic, consumptive, with a high mortality rate (in the absence of accurate treatment). As this case will be focused on extrapulmonary tuberculosis in children, it is necessary to mention that over 25% of patients (children) develop this complication and more than 10% of them do not survive.

Methods: We present the case of a 17 years old male with a history of operated pilocytic astrocytoma of the vermis, right cerebellum hemisphere and upper supratentorial obstructive hydrocephalus, suspected to have cysticercosis, which was admitted due to vomiting and generalized tonic-clonic seizures. Other associated symptoms were intracranial hypertension and global ataxia. Particularities of this case are the cerebral complications associated with tuberculosis, resulting in delayed treatment and no favorable outcome without a fast diagnosis.

Results: Over the course of treatment, the patient required ventriculo-peritoneal shunting, aggressive antibiotics, along with anti-inflammatory and anti-thermic medication. After performing multiple computed tomographies and cerebrospinal fluid examinations over the course of 4 weeks, the suspected final diagnosis of pulmonary tuberculosis and secondary meningo-encephalitis was confirmed, the patient was transferred to a regional hospital in order to undergo adequate treatment.

Conclusion: Over 9.6 million people have contracted tuberculosis in 2015, and over 25% of infected children also developed extra-pulmonary tuberculosis. In absence of prompt and adequate treatment, the mortality rates of this disease will rise (1.7 million deaths in 2015). Furthermore, prophylactic methods and their importance should be better explained to the population, in order to avoid contacting such an aggressive and consumptive disease.

Abbreviations: CRP - C reactive protein, CSF - Cerebro-spinal fluid, CT - Computed Tomography, GCS - Glasgow Coma Scale, GI - Gastro-intestinal, AST - Aspartateaminotransferase, ALT - Alaninaminotransferase, Hb - Hemoglobin, HCT - Hematocrit,

RÉSUMÉ

La tuberculose extrapulmonaire chez les enfants

Introduction: La tuberculose est une maladie très contagieuse, produite par *Mycobacterium tuberculosis* (*Bacille de Koch*). L'évolution de cette maladie est chronique, consomptif, avec un taux de mortalité élevé (à l'absence d'un traitement correcte). Comme ce cas va se concentrer sur la Tuberculose extrapulmonaire chez les enfants, il est nécessaire de préciser que plus de 25 % des malades (enfants) développent cette complication et plus de 10 % d'entre eux n'arrivent pas à survivre.

Méthodes: Le cas présent est celui d'un sexe masculin qui a 17 ans ayant des antécédents d'opération d'astrocytome pilocytique du vermis et de l'hémisphère du cervelet droit et d'hydrocéphalie obstructive du sus-tentorial supérieur, soupçonné d'avoir la cysticercose, qui a été reconnu en raison des vomissements et des crises tonico-cloniques généralisées. Les autres symptômes qui ont été associés étaient une hypertension intracrânienne et ataxie globale. Les particularités de ce cas sont les complications cérébrales associées avec la tuberculose, provenant des traitements à retardements et aucun résultat favorable sans un diagnostic rapide.

Résultats: Au cours du traitement, le patient a eu besoin d'une dérivation le ventriculo - péritonéale, d'antibiotiques agressifs, avec des médicaments anti inflammatoires et anti thermiques. Après avoir effectué plusieurs tomographies informatisées (tomodensitométrie) et d'examen du liquide céphalorachidien au cours de 4 semaines, le dernier diagnostic présumé de tuberculose pulmonaire et méningo-encéphalite secondaire a été confirmé, le patient a été transféré à un hôpital régional afin de suivre un traitement adéquat, car il avait très peu de chance de regagner sa santé.

Conclusion: Plus de 9,6 millions de personnes ont attrapé la tuberculose en 2015, et plus de 25% des enfants infectés ont également développé une tuberculose extrapulmonaire. En absence de traitement rapide et approprié, les taux de mortalité de cette maladie ne feront qu'augmenter (1,7 millions de décès en 2015). De plus, les méthodes prophylactiques et leur importance

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SP O₂ - O₂ saturation, TB - Tuberculosis, WBC - White Blood Cells, WCBC - White Blood Cell Count

Key words: Child Tuberculosis, Extra Pulmonary Tuberculosis, Astrocytoma, Seizure, Ataxia, Vomiting

devraient être mieux expliquées à la population, afin d'éviter tout contact avec une telle maladie agressive et consomptive.

Mots-clés: Tuberculose d'enfant, tuberculose extra pulmonaire, astrocytome, saisie, ataxie, vomissements.

INTRODUCTION

Extra pulmonary tuberculosis (TB) is a secondary manifestation of pulmonary TB which usually appears through hematogenous dissemination in the lymphatic nodes, kidneys, the epiphysis of long bones, vertebral body, juxtaependimal meninx and in the posterior apical parts of the lungs. (1,2) The incidence of extra pulmonary TB is higher in children, adolescents and young adults, with 28.3 new cases/100.000 people (in Romania). The patient was included in a retrospective study over a period of 6 months, conducted in Marie Curie Hospital Bucharest. (1,3)

CASE REPORT

A 17 year old male teenager patient, with a history of pilocytic astrocytoma of the vermis and right cerebellum hemisphere and upper supratentorial obstructive hydrocephalus was admitted to the Emergency Department of Bagdasar-Arseni Hospital for vomiting and generalized tonic-clonic seizures, intracranial hypertension and global ataxia. The general condition of the patient was critical (Glasgow coma scale-GCS- score 7, uncooperative, ataxia, fever 39°C). The patient was tachypneic, dyspneic, with a low level of oxygen saturation of 75%. He also presented upper gastro-intestinal (GI) bleeding. An emergency initial cranial Computed Tomography (CT) scan was performed which revealed the presence of multiple supra and infratentorial millimetric hypodense spontaneous lesions (characteristic for cerebral Cysticercosis). Three differential diagnoses were considered: Metastatic Astrocytoma, Cysticercosis and Tuberculomas.

In the first week after admission: the general condition of the patient remains critical with fever, aggravated neurological status: a lower GCS score (4p), convergent and divergent strabismus (alternating) and spontaneous nystagmus. As for chest auscultation, basal bilateral bronchi were found. Para clinical findings revealed hyponatremia (129 mEq/L), inflammatory syndrome (CRP 50.56 mg/L, fibrinogen 458 mg/dL), leukocytosis (WCBC 12.9 m/mm³) with hepatic reaction (TGO 157U/L, TGP 62U/L). The cerebrospinal fluid (CSF) analysis revealed a positive Pandy test along with glycorrachia (65.3 mg/dL), without bacteriological findings. A second CT scan is performed and although the edema still persists, there is a reduction in the number of cerebral lesions and so the double approach of the treatment at that time was to place a ventriculoperitoneal shunt along with administering specific medication (4,5): Antibiotics (Tazocin, Vancomycin, Gentamicin), Mannitol, Fenitoin, Fluconazole, anti-inflamma-

tory and antithermic drugs, Ringer, Glucose 5%, esomeprazol, and anti-TB drugs (table 1).

Over the course of the second week, the patient's critical condition persists, without fever. Neurologically, his GCS score is 7 and he presents flexion when a pain stimulus is applied, bilateral positive Babinsky, divergent strabismus and left lateral nystagmus. At auscultation the patient also presents bilateral bronchial rales and short periods of apnea. Para clinically, the patient is still hyponatremic (124 mEq/L), with a hematocrit level of 25.3%, leucocytosis (WBC 9.34 m/mm³), anemia (Hb 8.5 g/dL) and hepatic cytolysis (TGO 312 U/L, TGP 311 U/L). Microbiologically he is positive for KLEBSIELLA SPP. Imagistically, a new CT scan shows great reduction of the edema, but some areas with ischemic aspect can be observed along with nodular lesions in the brain, cerebellum and the brain stem.

During the third week of hospitalization the patient develops fever again (38.6°C) as his condition continues to be extremely critical. Neurologically, his GCS score is down to 6. Para clinically, Na is down to 122 mEq/L, with the hematocrit rising up to 33%. The cytological aspect of the spinal fluid is clear, Pandy reaction is negative, but the glucose level is high (40 mg/dl), as well as the protein level (355 mg/l). The latest CT scan shows a cerebrovascular accident (stroke) in the lenticular nucleus (fig. 5).

As we move on to the fourth week, the patient is in a very critical condition, with the fever spiking up to 39°C. Even though his Na level is up to 144 mEq/L, his glucose level is down to 81, hematocrit is down to 23% and his RBC, WBC and hemoglobin are down to 2,7 m/mm³, 5 m/mm³ and 5.7 g/dL respectively. He still presents an inflammatory syndrome (CRP 68.64 mg/L), although the hepatic cytolysis is now absent as TGO and TGP levels have returned to normal. Upon the examination of the spinal fluid, we find a positive Pandy reaction again, along with high levels of glucose (33 mg/dL) and proteins (797 mg/L). The patient also was positive for PSEUDOMONAS SPP. In addition to this, a microbiological examination of the patient's sputum reveals BAAR + (Ziehl-Neelsen coloration, Florescence).

The patient is discharged to a regional hospital with a diagnosis of primary pulmonary TB and secondary meningo-encephalitis. Over the course of the 4 weeks, the evolution of the patient has not been a favorable one (fig. 1, fig. 2, fig. 3, fig. 4).

DISCUSSION

According to the ATS (American Thoracic Society) there are 5 stages of infection with tuberculosis (6, 7):

- Exposure: the child had contact recently with a person with contagious TB; without physical signs or

Table 1 - Dosing of first line anti-TB drugs

Dosing of First-Line Anti-TB Drugs*					
Drug	Adults or Children	Daily†	Once/wk	2 Times/wk	3 Times/wk
Isoniazid	Children (maximum)	10–15 mg/kg (300 mg)	N/A	20–30 mg/kg (900 mg)	N/A
Rifampin	Children (maximum)	10–20 mg/kg (600 mg)	N/A	10–20 mg/kg (600 mg)	N/A
Rifabutin	Children	Dosing unknown	N/A	N/A	N/A
Rifapentine	Children	N/A	N/A	N/A	N/A
Pyrazinamide	Children (maximum)	15–30 mg/kg (2 g)	N/A	50 mg/kg (2 g)	N/A
Ethambutol	Children (maximum)	15–20 mg/kg (1 g)	N/A	50 mg/kg (2.5 g)	N/A

*Specific regimens

†Daily is considered either 5 or 7 days/wk. All dosing < 7 days/wk must be given as directly observed therapy.

N/A = not applicable.

Figure 1 – Blood cell count, Hb, HCT values

Normal Values
RBC: 4.7-6.1 m/mm³
WBC: 4-10 m/mm³
HCT: 38.8-50.0 %
Hb: 13.5-17.5 g/dL

Blood cell Count, Hb, HCT Values

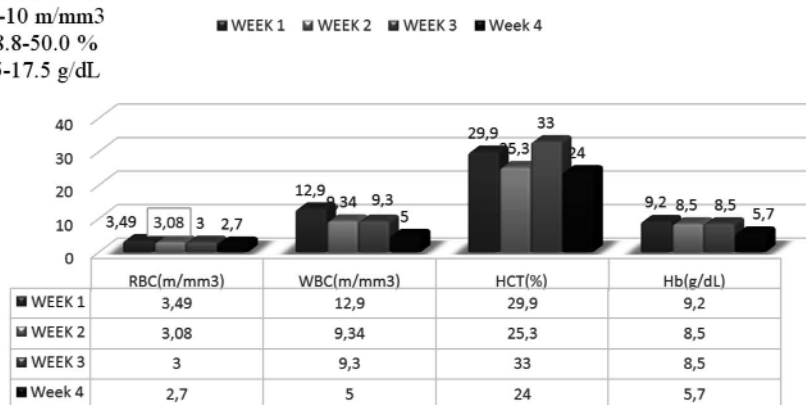
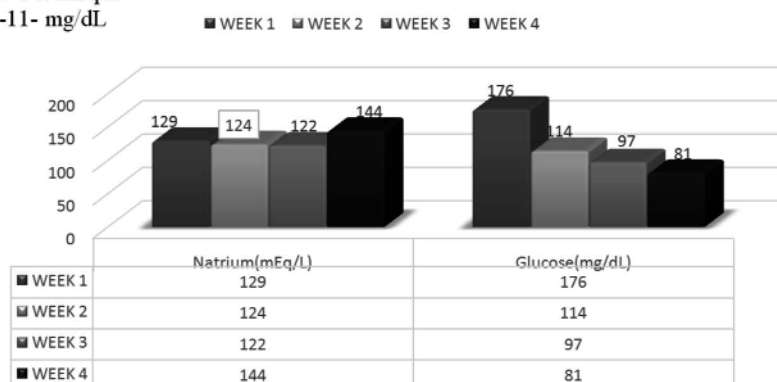


Figure 2 – Serum natrium and glucose values

Normal Values
Natrium: 136-145mEq/L
Glucose: 90-11- mg/dL

Serum Natrium and Glucose Values



- symptoms, IDR negative, chest X-Ray does not reveal changes;
- IDR +, without signs and symptoms, Chest X-Ray can reveal the primary complex;
- TB disease appears characterized by specific signs and symptoms due to location, radiographic abnormalities visible;
- Tuberculosis, without any actual disease, meaning

Figure 3 – CRP and Liver transaminases values

Normal Values
CRP: 0-10 mg/L
AST: <35 U/L
ALT: <35 U/L

CRP and liver transaminases values

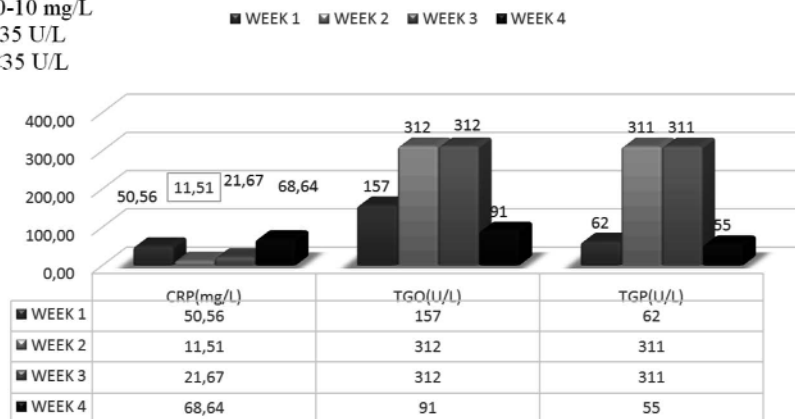
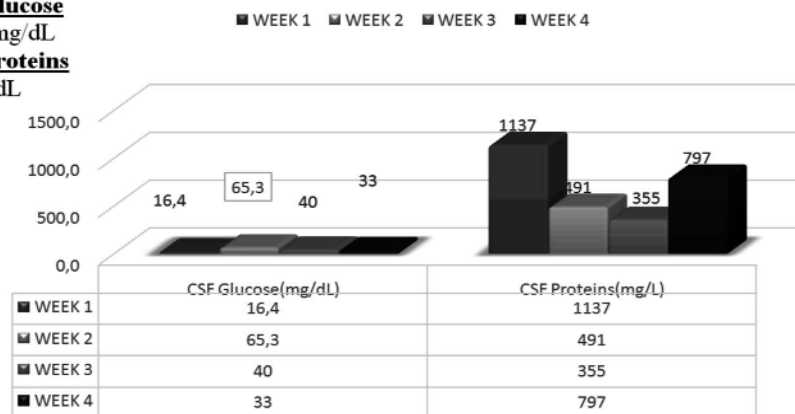


Figure 4 – CSF examination results

Normal Values
CSF Glucose
 45-80 mg/dL
CSF Proteins
 45 mg/dL

CSF examination Results



that the patient has a history of episodes of TB or radiological elements, stable, IDR + and negative bacteriology without exam changes suggestive at clinical examination;

- Tuberculosis is suspected but the diagnosis is pending (8, 9).

In regard to extra pulmonary TB, 25-30% of children with TB show extra pulmonary pathology, which includes the following: Peripheral lymphadenopathy, TB meningitis, millitary TB, bone TB, or in other exceptional places: medium ear, gastrointestinal tract, skin, kidney, ocular structures and pericarditis (it can also be an acute complication).

Of all these complications, TB meningitis is by far the most dangerous and aggressive:

- It develops in 5-10% of children under two years old(frequency below 1%);
- Insidious onset, sub-acute presentation: 3-6 months after the initial infection; non-specific symptoms: anorexia, weight loss, fever;
- After 1-2 weeks: vomiting, seizures; altered mental status, coma and death can occur despite prompt intervention;
- Neurological signs can be absent/ focal /generalized,

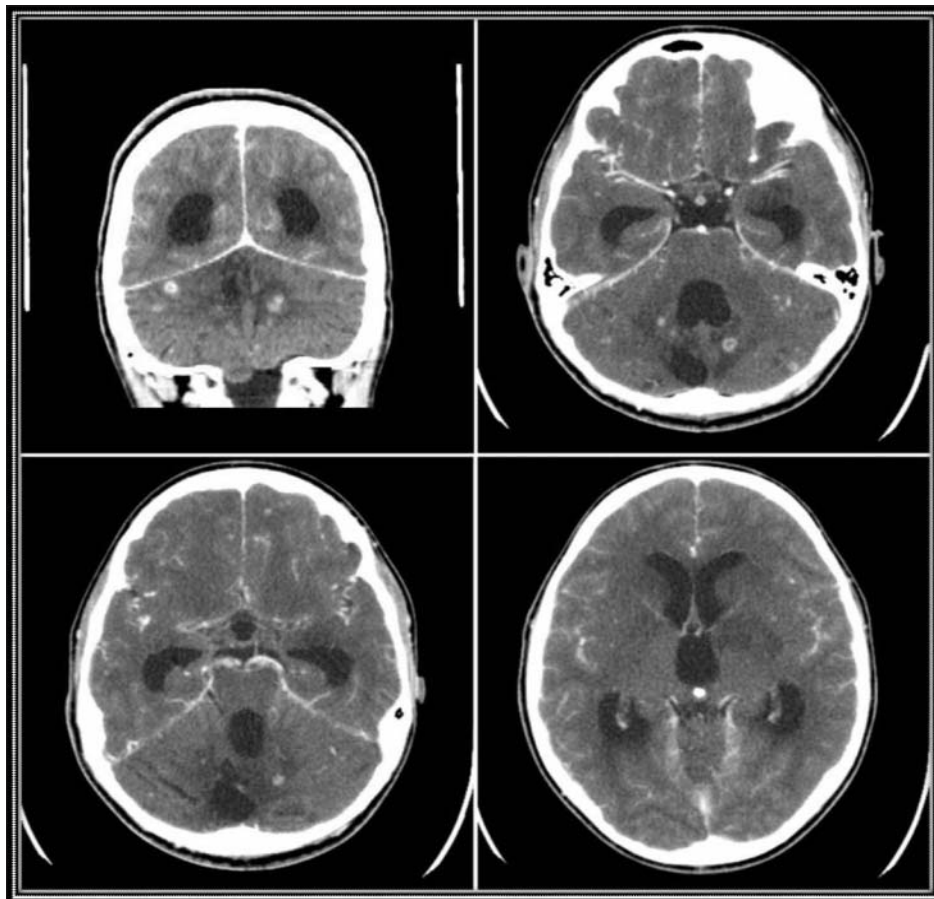
non-specific signs may occur;

- Nuchal stiffness, alteration of deep tendon reflexes, lethargy, and/or paralysis of cranial nerves; affects particularly the following nerves: VI but also II, IV, VII; at the eye exam: papillary edema, choroid tubers;
- The final stage with the major neurological defects: coma, seizures and paradoxical movements: paresis, paralysis in 1 or more segments; opisthotonus, +/- death;
- CSF: exudate, clear/opalescent normotensive, proteins, glucose, cultures often positive for *Koch Bacillus* (KB microscopy negative). (10,11,12)

The diagnosis of this disease usually comes too late due to the large number of unspecific symptoms which do not lead directly to pulmonary or extra-pulmonary TB. However, the methods of testing are widely available, and consist in:

1. Tuberculin cutaneous testing: it consists of an intradermal injection of antigens from strictly MTB (also called PPD = purified protein derivative) which causes a delayed hypersensitivity reaction due to local increase of lymphocytes and macrophages. After 72 hours, if the induration is larger than 10 mm, the test

Figure 5 – Week 3 CT



is positive for tuberculous infection. (13)

2. PCR testing: it is based on amplifying a unique sequence of *katG* gene present in members of the *Mycobacterium tuberculosis* complex: *Mycobacterium tuberculosis*, *Mycobacterium bovis*, *Mycobacterium africanum* and *Mycobacterium microti*. The major advantage is that results may come up within hours and not after 20-60 days. Where the clinical suspicion of TB is high, PCR is positive in 80-90% of tested respiratory specimens (pleural fluid and bronchial aspirates). The PCR method, in particular RTPCR, has the advantage of a rapid diagnosis, the treatment being established within the context of clinical suspicion. (14,15)

As tuberculosis is highly aggressive and has a high mortality rate in children, a method of prevention which is available to the large public would be vaccination. Prevention of TB is accomplished, as well as in other infectious diseases, through the increase of body specific resistance via vaccination (16,17). Studies on the vaccine's effectiveness have shown variable results: 15-20% up to 50-60% of those vaccinated were protected, which shows that BCG vaccine shelters against the development of the infection to disease but does not protect against tuberculosis infection. Of course there are certain contra indications: weight at birth < 2500 g, immunodeficient new born, those who are HIV + must be immunized, leukemia, lymphomas, malignancy, febrile

illness, 6 months after viral hepatitis, active TB. TB prevention also consists of prompt identification, treatment of patients with TB, education, treatment of the latent infection. (18)

CONCLUSION

TB manifests as an endemic disease at a global level, the number of cases being rather constant, with slight changes from year to year. However, due to the clinical, radiological, pathogenic and evolutive polymorphism of this disease (caused by the resistance of the mycobacteria in the organism) along with the lesional polymorphism (infiltrative lesions, necrosis) and poor adherence of basic prophylaxis rules, the number of TB cases has risen from 8.8 million in 2008 (1.5 million deaths), to 9.6 million in 2015 (1.7 million deaths). Romania is the 4th in Europe based on the prevalence of the disease, with 28.3/100.000 children infected (1 million globally) and an incidence of 70.2/100000. 8.3% of the new patients and 2.6% of readmitted patients develop extrapulmonary tuberculosis. The rate of mortality in Romania is 6.4/100000 patients, higher than the European mean of 5.3/100000 patients. (18,19)

Child vaccination is extremely important for prophylaxis of the infection, along with repeated diagnostic testing after exposure to BK. Even though the vaccine offers protection for 5 years, this period might be quite critical especially for

patients with a compromised immune system. The prognosis of our patient was initially unfavorable, but with effective treatment the patient has survived.

Even though, tuberculosis should not be such a wide spread disease throughout the world due to the availability of vaccination (BCG Vaccine) and readily available materials about care and prevention. However, this disease affects more and more people from wealthy countries due to the fact that people are ignorant to the importance of vaccination or believe that vaccines are harmful for their children, whether in the case of TB, if the new born is not vaccinated until the age of 1, the risk of infection rises considerably. (19)

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