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# РЕТРОСПЕКТИВНАЯ ОЦЕНКА ВЕРОЯТНОСТИ И ТЯЖЕСТИ ТУБЕРКУЛЕЗНОГО МЕНИНГИТА У ПОДРОСТКОВ И ВЗРОСЛЫХ НА ГОСПИТАЛИЗАЦИИ

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# RETROSPECTIVE ASSESSMENT OF PROBABILITY AND SEVERITY OF TUBERCULOUS MENINGITIS IN ADOLESCENTS AND ADULTS ON ADMISSION IN HOSPITAL

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**Резюме**. В статье рассматривается случай больного туберкулезным менингитом (ТМ) 16 лет, который находился на стационарном лечении в Республиканском научно-практическом центре пульмонологии и туберкулеза (РНПЦПТ) на 425 дней. В статье ставится задача обсудить степень вероятности туберкулезного менингита у одного и того же больного с использованием упомянутых в статье диагностических шкал.

**Ключевые слова:** Туберкулезный менингит, Диагностический индекс Thwaites, консенсусная система Ланцет, множественная лекарственная устойчивость, спинномозговая жидкость.

**Resume.** This article reviews the case of a 16-year-old patient with tuberculous meningitis (TM), who was admitted to the Republican Scientific and Practical Centre for Pulmonology and Tuberculosis for 425 days. The study aims to assess the probability of TM in the patient based on diagnostic scales mentioned in the article (Thwaites diagnostic scale and Lancet Consensus System).

**Keywords:** Tuberculous meningitis, Thwaites diagnostic index, Lancet consensus system, Multi-drug resistance, Cerebrospinal fluid.

**Actuality.** Tuberculous meningitis (TM) is the most severe form of extrapulmonary tuberculosis with high rate of morbidity and mortality (30-60%) [1]. Develops as an early or late complication of primary infection. Mortality is often associated with delayed diagnosis and treatment [2]. Symptoms and signs of the disease are not specific. Diagnostic scales with high specificity and sensitivity for detecting TM in adults are uncommon but helpful for early diagnosis of TM. For example, the Thwaites scale shows a sensitivity of 56% and specificity of 96% for diagnosing TM [5], while the Lancet consensus scale showed a satisfactory diagnosis of TM, with a sensitivity of 50% and specificity of 89.3% [6].

**Aim:** to assess the probability of TM and severity of TM in a 16-year-old adolescent girl hospitalized at the RSPCPT using assessment scales (Thwaites diagnostic index, 2004 and Lancet Consensus System, 2010) and clinical data of patient during hospital stay.

**Objectives**:

1. to assess the severity of TM in the patient, based on clinical data.
2. to assess the probability of developing TM using the Thwaites diagnostic index and the Lancet consensus system at admission.

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**Materials and methods.** Retrospective study of medical card of a 16-year-old girl hospitalized at the RSPCPT on 04.04.2013 from Pediatric infectious hospital with presenting symptoms of headache, vomiting, diarrhoea and fever for > 5 days.

In anamnesis: Patient had close periodic contact with bacterio-excrete person (Her father died of infiltrative pulmonary tuberculosis, in 2003).

On initial examination, patient had neck stiffness and slightly positive Kernig's sign. Chest X-ray of patient demonstrated interstitial foci in lungs at first and on later examination, disseminated foci in lungs were revealed.

MRI of brain first showed inflammation of right cerebral hemisphere, later on clinical picture of encephalo-myelitis in right side of occipital lobe was revealed with a single convulsive seizure in the acute period (28.07.13).

On ultrasound of abdomen, hepato-splenomegaly, reactive changes of liver vessel and signs of diffuse changes in parenchyma of pancreas and kidneys were revealed.

Patient received BCG vaccine on birth and a scar of 3 mm was present on shoulder. The results of Mantoux test which was performed in 2010, 2011 and 2012 showed positive tuberculin reaction with induration of 5mm, 5mm and 7mm respectively. Mantoux test was performed on hospitalization in 2013, showed negative tuberculin reaction.

Some of the most important findings seen in Cerebrospinal fluid (CSF) analysis of patient on initial admission includes transparent colourless appearance, decreased glucose in the CSF, elevation of protein and sharp increase of total CSF WBC count (115/µl ) (table 1)

**Tab. 1.** CSF analysis

| Date | Appearance | Protein (0.23-0.38g/l) | Glucose (2.5-4.4) | Pleocytes (5-10/µl) | Neutrophils | Lymphocytes |
|---|---|---|---|---|---|---|
| 25.03.13 | Clear/ Transparent | 0.68 g/l | 2.04 mmol/l | 115/µl | 64% | 38% |
| 28.03.13 | Clear/ Transparent | 0.8 g/l | 2.08 mmol/l | 132/µl | 84% | 16% |
| 04.04.13 | Clear/ Transparent | 0.7 g/l | 2.1 mmol/l | 86/µl | 43% | 54% |

On 25.03.13, segmented neutrophils in CSF were 64% and lymphocytes were 38% and later on 04.04.13, neutrophils reduced to 43% and lymphocytes increased to 54%. In complete blood count, neutropenia (34%) and eosinophilia (32%) were seen on 29.06.13.

Several bacteriological diagnostic tests were performed: Smear microscopy of induced sputum did not show presence of MTB. Sputum and urine culture (30.09.13 and 09.09.13 respectively) did not reveal any presence of bacteria but CSF culture revealed infrequent presence of MTB with very poor growth. Sputum Bactec (21.05.13) did not show any presence of bacteria while CSF Bactec (04.04.13) showed presence of MTB with drug resistance to Isoniazid (H), Streptomycin (S) and Amikacin (Am) and sensitive to Rifampicin (R), Pyrazinamide (Z), Kanamycin (Cm), Ethambutol (E). Later CSF culture (11.04.13) showed that the bacteria developed additional resistance to R and E, hence MTB in patient was Multidrug resistant (MDR).

Intensive phase of treatment was started on 05.04.13 with H (0.3), R (0.45), S (1.0), E (1.0), Z (2.0) but due to the development of resistance of MTB to most of the first line drug (except Z), the scheme of the treatment was changed (16.04.13) to second line drugs

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(Lfx-1.0, PAS-9.0 and Cs-0.5) plus Z (2.0). In the process of treatment with anti-TB drugs (ATD), patient developed itching and confluent bullous–popular rash on the inner surfaces of the limbs and abdomen, hyperaemia and swelling of the skin of the face at the 4th month of the disease. The adverse reactions of ATD developed, in the form of Quincke's edema and allergic vasculitis (04.07.2013). Methylprednisolone (Medrol) was also prescribed on 19.07.13 with a dose of 20mg/day to reduce the neurological complications and on 27.09.13, the dose of Medrol was reduced up to 2 mg per week. Later MTB became resistant to some second like drugs also like Am, Lfx and PAS. So, the final scheme of treatment was chosen for both intensive and maintenance phase of treatment: Z (1.6), Mfx(0.4), Pto (0.75), Cm (1.0) and Cs (0.75) and antihistamine drugs were prescribed in place of methylprednisolone.

Treatment was satisfactory, and well tolerated. Patient had positive clinic, laboratory (improvement of general blood analysis: decrease eosinophils, normalisation of ESR, normalisation of Band neutrophils) and x-ray dynamics. The patient was discharged (03.06.14) in satisfactory condition without any complaints (fever, headache, cough) and was transferred to ambulatory regime of treatment and then on sanatory regimen. On the basis of data obtained from the patient's case history, 2 diagnostic indices were evaluated retrospectively: Thwaites diagnostic index, tab.1 [3]; Lancet consensus system, tab.2 [4].

**Results and their discussion.** TM can't be definitively diagnosed based on history and clinical data alone. The symptoms of TM closely resemble that of subacute bacterial meningitis. The most predictive symptoms for TM are the duration of clinical symptoms mentioned above being more than 5 days. Increase in protein, decrease in glucose amount in CSF also indicates TM. In early stages of the disease, neutrophils in CSF predominated over lymphocytes but gradual predominance of lymphocytes over neutrophils indicates a long-term existence of TM and poor prognosis. CSF examinations microscopy and culture are considered gold standard in diagnosis of TBM but are not very sensitive because of low count of bacteria in CSF and difficulty in processing without sufficient amount (culture of CSF showed only occasional presence of MTB because of low number of bacteria). The presence of MDR MTB in culture and neurological manifestations like seizures indicates the high severity of TM . Use of adjuvant therapy like Prednisolone improved the neurological symptoms significantly in patient but doses were reduced gradually to prevent the development of potential side effects. Patient was assessed on Thwaites diagnostic index on the basis of 5 parameters: Age, WBC, Complaint duration, CSF WBC, CSF WBC% PNL and patient had a resulting rate score of -5 which strongly suggests etiology of *M. Tuberculosis* and excludes etiologies of other bacteria, tab.2.

**Tab. 2.** Thwaites diagnostic index on admission

| Parameters | | | Cut off Index | | Patient's score |
|---|---|---|---|---|---|
| Age | ≥36 | <36 | 2 | 0 | 0 |
| WBC in blood | ≥15000/mm$^3$ | <15000/mm$^3$ | 4 | 0 | 0 |
| Complaint duration | <6 days | ≥6 days | 0 | -5 | -5 |
| CSF WBC | ≥900/ mm$^3$ | <900/ mm$^3$ | 3 | 0 | 0 |
| CSF WBC % PNL | ≥75 | <75 | 4 | 0 | 0 |
| Total points of investigated patient | | | | | **-5** |
| ***Assessment criteria**:* If Total score ≤4 = TM; If >4= bacterial meningitis of other origin. | | | | | |

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Patient was also assessed on Lancet consensus system on the basis of 20 parameters which includes Clinical criteria, CSF criteria, CNS imaging criteria and evidence of tuberculosis elsewhere and the patient had a resulting rate score of 13 which indicates probable TM, tab.3.

**Tab. 3**. Lancet consensus system

| **1) Clinical criteria** | (Max. category score = 6) | Patient score |
|---|---|---|
| Symptom duration > 5 days | 4 | 4 |
| Systemic symptoms suggestive of tuberculosis (one or more of the following): weight loss (or poor weight gain in children), night sweats, or persistent cough for more than 2 weeks | 2 | 0 |
| History of recent (within past year) close contact with an individual with pulmonary tuberculosis | 2 | 0 |
| Focal neurological deficit (excluding cranial nerve palsies) | 1 | 0 |
| Cranial nerve palsy | 1 | 0 |
| Altered consciousness | 1 | 0 |
| Total points in this criterion | | 4 |
| **2) CSF criteria** | (Max. category score = 4) | Patient score |
| Clear appearance | 1 | 1 |
| Cells: 10–500 per μl | 1 | 1 |
| Lymphocytic predominance (> 50%) | 1 | 0 |
| Protein concentration > 1 g/L | 1 | 0 |
| CSF to plasma glucose ratio of less than 50% or an absolute CSF glucose concentration less than 2·2 mmol/L | 1 | 0 |
| Total points in this criterion | | 2 |
| **3) Cerebral imaging criteria** | (Max. category score = 6) | Patient score |
| Hydrocephalus | 1 | 1 |
| Basal meningeal enhancement | 2 | 0 |
| Tuberculoma | 2 | 0 |
| Infarct | 1 | 0 |
| Pre-contrast basal hyper density | 2 | 0 |
| Total points in this criterion | | 1 |
| **4) Evidence of tuberculosis of other locations** | (Max. category score = 4) | Patient score |
| Chest radiograph suggestive of active tuberculosis: (signs of TB = 2; miliary TB = 4) | 2/4 | 2 |
| CT/ MRI/ ultrasound evidence for tuberculosis outside the CNS | 2 | 0 |
| AFB identified or MTB cultured from another source | 4 | 4 |
| Positive commercial MTB NAAT from extra-neural specimen | 4 | 0 |
| Total points in this criterion | | 6 |
| Total points of investigated patient | | 13 |
| ***Assessment criteria:*** 1) Definite TM = Acid Fast Bacilli (AFB) in CSF smear, culture or on histopathology of brain or spinal cord, NAAT -Nucleic acid amplification test<br>*2)* Probable TM = ≥12(if CNSimaging available), ≥10(if CNS imaging not available).<br>*3)*Possible TM= *6-11(*if CNS imaging available), 6-9(if CNS imaging not available). | | |

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**Conclusions:**

1. Tuberculous meningitis is a serious disease with high rate of mortality and permanent neurological manifestations. Diagnosing TM is difficult due to many reasons like: diversity of clinical symptoms, low count of bacteria in CSF makes it hard to detect the bacteria in culture and microscopy.

2. CSF examinations microscopy and culture are considered gold standard in diagnosis of TM and should be done immediately when TM is suspected before appearance of neurological symptoms.

3. The use of scoring indexes like Thwaites diagnostic index and Lancet consensus system showed successful results in predicting high chances of TM.

4. By evaluating the medical record, it can be concluded that the presence of MDR MTB in culture, neurological manifestations complicated by the development of encephalomyelitis and the appearance of a single convulsive seizure, indicate a high severity of TM.

5. The difficulties in the management and selection of the optimal chemotherapy regimen for the patient were due to presence of MDR-MTB with gradual development of multidrug resistance to first- and second-line ATD and due to the development of adverse ATD reactions in the form of allergic vasculitis and Quincke's edema.

6. To prevent the development of neurological complications, adjuvant therapy like usage of corticosteroids in early phase of treatment have showed very good results.

7. The treatment of TM remains a challenging task because it is hard to treat MDR MTB and prevent the development of neurological and allergic complications simultaneously.

8. Well-coordinated work, professionalism of specialists and competent medical tactics allowed to cope with the extremely severe, complicated course of TM and the patient in a satisfactory condition was discharged to the outpatient treatment, then to the sanatorium and home.

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