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Tuberculous meningoencephalitis in patient co-infected with herpes simplex virus

Objective — to pay attention of clinicians to sterile meningoencephalitis, which in fact can be caused by mycobacteria tuberculosis.

Materials and methods. The routine lab methods were used in the study. The bacterial and viral DNA sequences were quantified by real-time PCR. Smear microscopy using the Ziehl-Neelsen stain, and CSF pellet cultivation on the Lowenstein-Jensen medium were used for searching of *M. tuberculosis*.

Results and discussion. A young woman was admitted to our hospital because of fever, headache and hallucinations, and meningeal symptoms. Pleocytosis, decreased level of glucose, HSV-1 DNA and antibodies to the virus were found in CSF sample. Although antibiotics and acyclovir were administered, fever, hallucinations and meningeal signs intensified. A second CSF sample contained higher level of cytosis and a «spider-web» cloth (SWC). So, tuberculosis was regarded as the most likely cause of the disease. Later, when *M. tuberculosis* DNA was revealed in CSF, the diagnosis was confirmed. The patient started receiving antituberculous treatment with good effect.

Conclusions. The possibility of latent involvement in the process of *M. tuberculosis* should be kept in mind in any cases of sterile meningoencephalitis. An empiric trial of antituberculosis therapy may be useful in other cases of apparently idiopathic meningoencephalitis.

Key words

Tuberculosis, meningoencephalitis, herpes simplex virus.

1. Introduction

Tuberculous meningoencephalitis (TBM) is one of the most serious clinical forms of extra-pulmonary tuberculosis (TB) with a high mortality rate and disabling neurological sequelae [4]. TBM often has atypical onset and evolution, highly heterogeneous and unspecific clinical symptoms that result in a delayed diagnosis. Prognosis therefore is poor, despite adequate treatment. Often tuberculosis and TBM are observed in people with immunosuppression and, above all, HIV-infected. Beside HIV, other pathogens can suppress immunity and accompany TB. Below we present the case of TBM in a young adult woman co-infected with HSV-1/2.

2. Case Presentation

Patient information

A 22-year-old woman was presented to The Center of Infectious Disorders of the Nervous System (CIDNS, Kyiv, Ukraine) in March 2017 with dizziness, 2-week history of fever, severe frontal headache, a sense of «heaviness» in the head, weakness, memory impairment, cervical and lumbar pain and vomiting during the last 3 days. The patient was in good health until a month before admission to our clinic. After severe stress specific symptoms developed. She was admitted to the local hospital, where she was treated with anti-inflammatory and neuroprotective drugs for 2 weeks. A umbar puncture (LP) was not performed. Since her fever and intoxication symptoms worsened, she was presented to CIDNS for further follow-up and treatment.

Personal history

The patient denied TB and previous disorders of the CNS. She had no history of immunosuppression.

Clinical findings

On admission, general condition of the patient was severe. Clinical manifestations observed included: fever, headache, weakness. She also experienced visual and auditory hallucinations (critical). The patient presented cranial nerve dysfunctions (rightward-ptosis, eyelid tremor, diplopia), left-beating nystagmus, smoothed leftward-nasolabial fold, mitigated deep tendon reflexes in her lower extremities, reduced muscular strength on the leftward, tremor of the hands during the complicated Barre — test, and dysmetria, which was observed on the finger-to-nose test. Lasseg, Nery, Gordon, Stryumpel, Chaddok, Pussep, Babinsky signs were positive for one or both sides in addition to a stiff neck and meningeal symptoms (Kernig/Brudzinsky).

Diagnostic focus and assessment

A blood test revealed small neutrophilic leukocytosis. CSF analysis showed significant pleocytosis of 247 cells/mm^3 (mononuclear cells, 88 %; PMNC, 12 %); glycorrhachia, 1.7 mmol/L; proteinorachia, 0.99 g/L; and CSF/blood glucose ratio, 0.35. HSV-1 DNA and HSV-specific IgG were also revealed in the CSF sample. No other DNA no antibodies to viral and bacterial proteins were detected in the spinal fluid, and blood. Acid-fast bacilli were not found in the smear. CSF culture was sterile. MR brain imaging in T2W, FLAIR, and T1W mode showed a mild expansion of the perivascular space in the projection of basal nuclei of both hemispheres. The regions of hyper intensive MR signal on T2 mode were located in various parts of the right hemisphere (figure).

Taking into account the data, a suspected diagnosis was made: HSV-associated meningoencephalitis. Cefoperazone/sulbactam, dexamethasone, acyclovir, and ademetionine were administered. As a result, the patient's state improved somewhat, however, the second CSF sample obtained 7 days after the collection of the first one showed higher level of cytosis, 317 (85 % lymphocyte, 15 % PMNC), and lower level of glucose, 0.6 mmol/L. Besides, a «spider-web» cloth (SWC, specific fibrin film) was firstly detected. The chest CT was normal. Accordingly, treatment was completed with isoniazid, ethambutol, rifampicin and levofloxacin. Soon cytosis began to decrease (189 WCC/ml), glucose to increase (1.2 mmol/L), and neurological signs to regress. Finally, after a week of the second sampling in the third CSF probem. Tuberculosis DNA was found. It allowed the suspected diagnosis

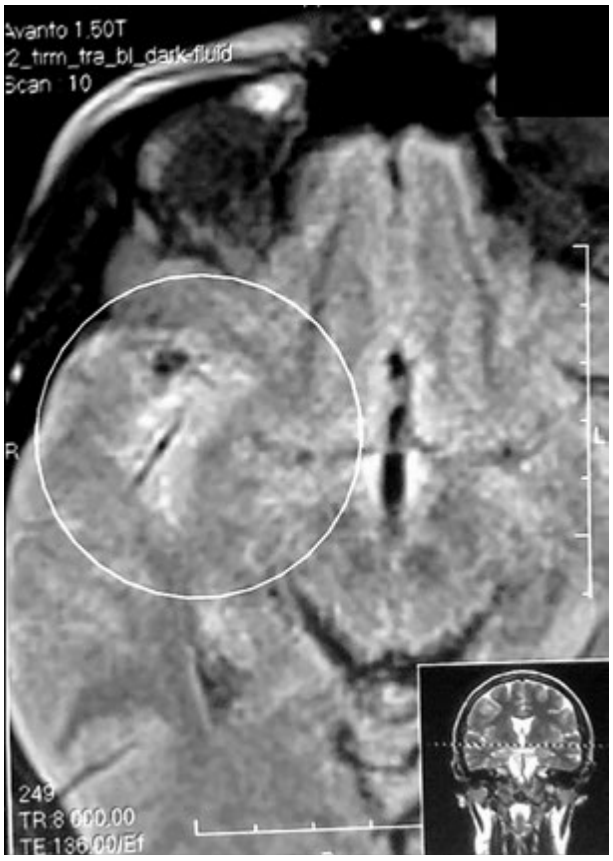

Figure. **T2 weighted image of MRI brain showing areas of mild increased signal in the right parietal lobe (made soon after admission)**

to be changed on tuberculous meningoencephalitis. Therefore, cefoperazone/sulbactam, and acyclovir were stopped, and streptomycin was added instead. During the next 5 weeks, the complete regression of neurological symptoms (except for finger-to-nose test) was observed. The patient was discharged for outpatient treatment 05/24/2017 with a recommendation for control survey after five-six months. 09/12/2017 control examination was made. There were no complaints, no neurological/meningeal signs. A CSF sample contained 15 cells/mm^3, 0.66 g/L of protein, 2.7 mmol/L of glucose, IgG to HSV-1/2, and SWC. No KB-DNA was detected. MRI brain contained no pathologic foci. The patient was recommended to continue anti-TB treatment for at least a year with the checkup.

3. Discussion

Tuberculous meningoencephalitis is a rare but extremely dangerous form of tuberculosis. Only the early treatment allows a patient's recovery. The case presented above highlights the challenges in the diagnosis of TBM. It is of interest primarily because the treatment was an important imperative of the correct diagnosis. Indeed, initially we classified the case as HSV-1-associated meningoencephalitis.

This conclusion was absolutely legitimate because it was based on rigorous, formal criteria: presence of HSV-1 DNA and antibodies to the virus in the sterile CSF. Moreover, the following two weeks' therapy with acyclovir results in complete virology response but not neurological recovery. On the contrary, the patient's state worsened. So, we were forced to revise the treatment strategy: acyclovir was canceled and set of anti-tuberculosis drugs was introduced. Prerequisites for that were high cytosis and appearance of SWC. An empirical treatment soon led to positive dynamic in the patient's state. We think that the reactivation of persistent HSV-infection was triggered by the underlying disease. However, relapse of the HSV-infection had no effect on the pathological process in the brain.

It is known, laboratory diagnosis of TBM based on the results of the routine CSF analysis and imaging data is often inadequate in making a correct diagnosis or even leads to a miss diagnosis. In addition, the diagnosis should be quick, as it is vital [2]. Smear microscopy using the Ziehl-Neelsen stain is the rapid but low sensitive method. Propagation of *M. tuberculosis* on the Lowenstein-Jensen medium, is very slow, making it impractical for prompt diagnosis [3]. PCR-based methods are the best for rapid and definitive diagnosis of CNS tuberculosis. We used the GeneXpert test with sensitivity of 59.3 % [1]. In the case presented here, the repeated conventional (microscopy, bacteriology) and even modern (PCR) tests for tuberculosis revealed firstly to be negative. So, the diagnosis ex juvantibus was the only choice. Later *M. tuberculosis* DNA was found in some CSF samples that confirmed the diagnosis.

4. Conclusion

In our case report, the treatment allowed us to establish the correct diagnosis; fortunately, we could perform the procedure before the patient developed a critical status. The published evidence and presented here our clinical experience suggest the importance and urgent need to develop new specific and highly sensitive methods to further improve the diagnosis of TBM to reduce mortality.

No conflicts of interest. Participation of authors: concept development, processing of material, text writing — P.A. Dyachenko, A.G. Dyachenko; collection of material — P.A. Dyachenko.

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Туберкульозний менінгоенцефаліт у хворої, інфікованої вірусом простого герпесу

Мета роботи — звернути увагу лікарів на стерильні менінгоенцефаліти, які насправді можуть бути викликані мікобактеріями туберкульозу.

Матеріали та методи. В роботі були використані рутинні лабораторні методи. Послідовності бактеріальної та вірусної ДНК кількісно визначали за допомогою реал-тайм полімеразної реакції. Для пошуку *M. tuberculosis* осад СМР окрашували за Ziehl-Neelsen і культивували на середовищі Lowenstein-Jensen.

Результати та обговорення. До нашої лікарні була доставлена молода жінка зі скаргами на лихоманку, головний біль та галюцинації. В неї також спостерігались менінгеальні симптоми. У зразку спинномозкової рідини (СМР) відмічений плейоцитоз, знижений рівень глюкози, а також була виявлена ДНК ВПГ-1 та антитіла до вірусу. Попри застосування антибіотиків та ацикловіру стан пацієнтки погіршувався. Другий зразок СМР, отриманий через тиждень після першого, характеризувався більш високим рівнем цитозу та наявністю фібринового згустка, який часто зустрічається при туберкульозному менінгіті. Отже, туберкульоз став вважатися найбільш ймовір-

ною причиною захворювання. Виявлення ДНК *M. tuberculosis* у третьому зразку СМР підтвердило діагноз. Пацієнтка почала отримувати протитуберкульозне лікування з гарним ефектом.

Висновки. У будь-яких випадках стерильного менінгоенцефаліту слід мати на увазі можливість прихованого втручання в процес *M. tuberculosis.* Емпіричне призначення протитуберкульозної терапії може бути корисним у випадках ідіопатичного менінгоенцефаліту.

Ключові слова: туберкульоз, менінгоенцефаліт, вірус простого герпесу.

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Туберкулезный менингоэнцефалит у больной, инфицированной вирусом простого герпеса

Цель работы — обратить внимание врачей на стерильные менингоэнцефалиты, которые на самом деле могут быть вызваны микобактериями туберкулеза.

Материалы и методы. В работе были использованы рутинные лабораторные методы. Последовательности бактериальной и вирусной ДНК количественно определяли при помощи реал-тайм полимеразной цепной реакции. Для поиска *M. tuberculosis* осадок СМЖ окрашивали по Ziehl-Neelsen и культивировали на среде Lowenstein-Jensen.

Результаты и обсуждение. В нашу больницу была доставлена молодая женщина с жалобами на лихорадку, головную боль и галлюцинации. У нее также наблюдались менингеальные симптомы. В образце спинномозговой жидкости (СМЖ) отмечен плейоцитоз, пониженный уровень глюкозы, а также была обнаружена ДНК ВПГ-1 и антитела к вирусу. Несмотря на применение антибиотиков и ацикловира состояние пациентки ухудшалось. Второй образец СМЖ, полученный через неделю после первого, характеризовался более высоким уровнем цитоза и наличием фибринового сгустка, который часто встречается при туберкулезном менингите. Итак, туберкулез стал считаться наиболее вероятной причиной заболевания. Обнаружение ДНК *M. tuberculosis* в третьем образце СМЖ подтвердило диагноз. Пациентка начала получать противотуберкулезное лечение с хорошим эффектом.

Выводы. В любых случаях стерильного менингоэнцефалита следует иметь в виду возможность скрытого вмешательства в процесс *M. tuberculosis.* Эмпирическое назначение противотуберкулезной терапии может быть полезным в случаях идиопатического менингоэнцефалита.

Ключевые слова: туберкулез, менингоэнцефалит, вирус простого герпеса.

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