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Benigh Reccurent Lymphocytic Meningitis (Mollaret Meningitis): a Case Report

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ABSTRACT The article reports a clinical case of a patient with four recurring episodes of headache, nausea and focal neurological symptoms (hemiparesis, sensorimotor aphasia, adversive epileptic seizures) with a rapid onset of remission. The clinical picture of the disease was supplemented with lymphocytic pleocytosis and cell-protein dissociation in the cerebrospinal fluid, which allowed to diagnose benign recurrent lymphocytic meningitis (Mollaret meningitis) and to conduct pathogenetic therapy.

The aim of this work is to improve the diagnosis of rare Mollaret meningitis.

Keywords: recurrent meningitis; recurrent benign lymphocytic meningitis; Mollaret meningitis

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BP — blood pressure
CMV — cytomegalovirus
CSF — cerebrospinal fluid
CT — computed tomography
DNA — deoxyribonucleic acid
EBV — Epstein-Barr virus
EEG — electroencephalography
EMS — emergency medical service
HR — heart rate
HSV — herpes simplex virus
IgG — immunoglobulin G
NSAIDs — nonsteroidal anti-inflammatory drugs
PCR — polymerase chain reaction
RR — respiratory rate
TIA — transient ischemic attack

BACKGROUND

Recurrent meningitis is characterized by recurring episodes of acute inflammation of the meninges, followed by periods of complete absence of symptoms and pathological changes in the cerebrospinal fluid. The causes of recurrent meningitis are sinusitis, mastoiditis, post-traumatic bacterial meningitis, Mollare meningitis, systemic lupus erythematosus and tumors such as epidermoid cyst and craniopharyngioma [16].

Recurrent benign lymphocytic meningitis of unknown etiology was first described by the French neurologist P. Mollaret in 1944 [1]. Therefore, the eponym "meningitis Mollare" began to be used to refer to the syndrome, which is also known as benign recurrent aseptic meningitis, benign recurrent endothelial-leukocyte meningitis, benign recurrent meningitis. This disease occurs mainly in young people, although clinical cases are described in patients from 5 to 57 years [2].

The clinical picture is characterized by remitting attacks, manifested by headache, meningeal syndrome, myalgia, and sometimes nausea and vomiting. The duration of the attack is short and ranges from 1 to 3 days. Examination reveals stiff neck, Kernig and Brudzinskiy symptoms. Transient neurological disorders in the form of epileptic seizures, diplopia, dysarthria, balance disorders, facial nerve lesions, anisocoria, feet pyramidal signs and consciousness disorders are also described. Fever is usually moderate, but can reach high numbers (up to 40 ° C) [3]. In approximately 30% of cases, non-specific symptoms in the form of paresthesia, neuropathic pain and arthralgia precede meningitis recurrence [8, 9]. If these symptoms do not fully regress, benign recurrent lymphocytic meningitis is eliminated [17]. The disease is usually resolved independently for 3–5 years, but there are reports of a longer course [4].

Currently, HSV-2 (Herpes Simplex Virus-2) is considered as the most likely cause of meningitis. About 84% of cases are Herpes Simplex Virus-2. More rarely, HSV-1 (Herpes Simplex Virus-1), HSV-6 (Herpes Simplex Virus-6), and toxoplasma are suggested as etiological factors [4, 5]. The pathogenesis is associated with reactivation of latent herpetic infection in sensory ganglia and retrograde spread of viruses with CSF. HSV-1 usually persists in the ganglion of the trigeminal nerve, HSV-2 is more often found in the sacral spinal nodes. Reactivation of HSV-1 is clinically manifested by orofacial herpes, less commonly by stomatitis, keratoconjunctivitis, and genital herpes. Reactivation of HSV-2 is manifested by recurrent genital herpes [6, 13]. But most often the reactivation of herpes infection occurs asymptomatically with the release and spread of viruses. This may be the cause of recurrent lymphocytic meningitis [12].

Historically, one of the diagnostic criteria for Mollare meningitis is the absence of the pathogen in the cerebrospinal fluid (CSF) [7]. However, with the advent of modern diagnostic methods, such as the polymerase chain reaction (PCR), it has become possible to identify herpes viruses in cerebrospinal fluid in patients with this disease [18]. Also on the first day of the onset of an attack, large cells of monocyte-macrophage origin (Mollare endothelial cells) can be found in the cerebrospinal fluid, using a Papanicolaou stain. Lymphocytic pleocytosis and moderate increase in protein levels appear later, The glucose concentration in the liquor is normal. Such changes in CSF are not specific and can be observed in other viral meningitis, for example, in West Nile fever [14, 15].

Mollare meningitis should be differentiated with recurrent bacterial, viral and fungal meningitis, sarcoidosis, echinococcal (hydatid) cyst, intracranial tumors, Behcet's disease and Vogt-Koyanagi-Harada syndrome. The last two diseases, among other signs, are characterized by significant lesions of the skin and eyes.

The full recovery of patients with Mollare meningitis usually occurs without specific treatment. The acute condition is suppressed by administration of colchicine, glucocorticosteroids, or nonsteroidal anti-inflammatory drugs (NSAIDs) [3]. However, due to the low prevalence of the disease, randomized clinical trials have not been conducted to evaluate the effectiveness of these drugs in the treatment of Mollare meningitis. Detection of DNA-containing herpes viruses in cerebrospinal fluid or immunoglobulin M (IgM) in the blood allows to prescribe antiviral therapy with acyclovir [10].

MATERIAL AND METHODS

We present our own clinical observation of recurrent serous meningitis, probably associated with chronic herpetic infection.

A 28-year-old male patient N. arrived on March, 3 in 2016 from Magadan, where he worked on a rotational basis. Suddenly, a significant bursting headache appeared, which the patient associated with acclimatization. He took non-narcotic analgesics, which gave a slight improvement. On March 24, 2016 the patient again experienced the bursting headache, numbness and weakness in the left extremities, nausea. Subsequently, complete regression of focal neurological symptoms was observed for 2 hours, but the headache persisted, no increase in body temperature was noted. He did not seek medical care. On April 1, 2016, a similar episode of severe headache, numbness and weakness in the left extremities repeated, with complete regression of focal neurological symptoms for 1 h. The EMS brigade brought the patient to Research Institute — Regional Clinical Hospital No. 1 n.a. Prof. S.V. Ochapovsky.

At the time of examination by a neurologist in the emergency department there were complaints of nausea, headache, and general weakness.

Objectively: the general condition of moderate severity. Active position. Normostenic constitution. No peripheral edema. Body temperature 37.1–37.4° C. Vesicular breathing, RR 17 per min. No wheezing. Stable hemodynamics, BP

126/87 mm Hg. Clear, rhythmic heart sounds. HR 70 beats/min. Soft abdomen, painless on palpation. Independent urination.

Neurological status: fully conscious. The verbal contact is fully available. The speech is not impaired. No meningeal signs. Pupils D=S, pupil photoreactions preserved. No nystagmus. Symmetrical face. Swallowing not impaired (according to the test for swallowing). The tongue in the midline. Active movements in the limbs. Normal muscle tone. Strength in the limbs corresponds to 5 points in all muscle groups. Brisk deep reflexes D=S. No pyramid signs. No sensitivity, coordinator and pelvic disorders.

The CT scan of the brain was performed, revealing no extensive or focal intracranial processes. In general clinical blood tests significant deviations were not detected.

The patient was hospitalized in the intensive care unit and resuscitation of the neurological department for dynamic observation with a diagnosis of a transient ischemic attack in the right carotid system. Neuroprotective, infusion and antiplatelet therapy was precribed.

On April 3, 2016 at 11p.m. a state of moderate severity with negative dynamics in the form of the development of sensorimotor aphasia, right-sided central faciobrachial paresis was recorded. The condition was regarded as a repeated acute violation of cerebral circulation in the left carotid system. According to emergency indications, computed tomography of the brain was performed: no volume, focal processes were detected; cerebral angiography was performed: no arteriovenous malformation, arterial aneurysms, hemodynamically significant obstacles to the blood flow, venous outflow was not disturbed. The hours later, the condition worsened, the significant psychomotor arousal developed. Adverse focal epileptic seizures with secondary generalization were appeared. The patient was transferred to the intensive care unit, due to adequate independent breathing, artificial ventilation was not performed.

April 4, 2016:

- general clinical, biochemical blood tests, coagulogram: no abnormalities;
- magnetic resonance imaging of the brain, magnetic resonance angiography of the cerebral veins: no ischemia, venous sinus thrombosis of the brain;
- electroencephalography (EEG): gross changes in the cortical rhythmics of a dysregulatory type were recorded with signs of middle structures involvement and a significant focus of epileptic activity in the right frontal-temporal-central region;
- diagnostic lumbar puncture, CSF study: CSF colorless, transparent, cytosis 256/3 (lymphocytes 99%, neutrophils 1%, erythrocytes 5-6-10 in sight, altered). Protein 0.49 g/l, glucose 4.91 mmol/l, chlorides 124 mmol/l, potassium 2.6 mmol/l, sodium 143 mmol/l, no fibrin.
- CSF study by PCR: Mycoplasma hominis, HSV (Herpes Simplex Virus) type 1, 2, 6, CMV (cytomegalovirus), EBV (Epstein-Barr virus), Enterovirus, Candida albicans, Mycobactrium tuberculósis, Toxoplasma gondii, Haemophilus influence, Streptococcus pneumoniae, Neisseria meningitidis, Borrelia — not detected.
- EIA: IgG to NA EBV 23.69 index (N 0–1), IgG to CMV 13.97 index (N 0–1), IgG to Herpes simplex 24.16 index (N 0–1), IgG Ch. Pneumoniae weakly positive, titer 1/10, IgG Borrelia not detected.

Preliminary diagnosis: “Serous meningitis of unknown etiology. Symptomatic epilepsy with focal adverse seizures of secondary generalization. "

The patient underwent antiepileptic therapy (Depakine chrono 1,500 mg/day), anti-inflammatory hormone therapy (Dexamethasone 16 mg/day). On the background of treatment, from 05.04 to 11.04.2016, there was a positive trend, there were no focal neurological symptoms and epileptic seizures. Periodically, the patient was euphoric, complained of a headache. On April 7, 2016 the patient was transferred to the ward due to a stable condition. On April 11, 2016 the lumbar puncture was performed. In the general analysis of CSF: cerebrospinal fluid is colorless, transparent, cytosis 443/3 (lymphocytes 94%, neutrophils 5%, monocytes 1%), protein 1,020 g/l, glucose 3.79 mmol/l.

On April 14, 2016, the patient repeatedely experienced the numbness in the left leg with a transition to the left hand, left half of the face, then to the right foot with a complete regress of symptoms 20 minutes later. General analysis of CSF on April 15, 2016: increased cytosis up to 592/3 (86% lymphocytes).

By the decision of the consultation, the final clinical diagnosis was made: "Benign recurrent lymphocytic Mollare meningitis." The patient continued taking Depakine chrono 1,500 mg/day and anti-inflammatory therapy (Dexamethasone 16 mg/day, Indomethacin 150 mg/day).

Over the next week, the state stabilized, the patient did not complain, independently actively moved within the department. In the neurological status: cerebral, focal symptoms not identified. EEG of April 18, 2016: against the background of moderate disorganization of the cortical rhythmics, there is a focus of paroxysmal activity in the frontal-central-temporal regions on the right. Typical epileptic activity at the time of the study was not detected. General analysis of the CSF on April 20, 2016: colorless, transparent, cytosis 106/3 (lymphocytes 89%), protein 0.34 g/l, glucose 4.21 mmol/l. The patient was discharged in satisfactory condition on the 21st day of hospital stay. The observation of a neurologist at the place of residence is recommended.

DISCUSSION

Currently, Mollare meningitis remains insufficiently studied and rarely occurring disease, because most often it is diagnosed by exclusion. Low awareness of clinicians in relation to this disease leads to the appointment of unjustified therapy.

The gold standard of diagnosis is the study of CSF using PCR, which confirms the presence of the genetic material of the herpes viruses with 95% sensitivity and 100% specificity [9]. Herpes Simplex Virus-2 is the most frequently identified etiological agent of benign recurrent lymphocytic meningitis [6]. If PCR is negative, there are criteria suggested by Bruyn et al. (Table) [11].

Table

Diagnostic criteria for Mollare meningitis

1.	Recurrent episodes of severe headache, meningism, fever .
2.	Transient focal neurological symptoms (in 50% of patients) .
3.	Spontaneous remission of symptoms .
4.	Asymptomatic periods lasting from several weeks to several months .
5.	Lymphocytic pleocytosis in the cerebrospinal fluid.
6.	The causative agent is not identified in the cerebrospinal fluid.

CONCLUSION

In the above clinical case, the patient had 4 recurrent episodes of headache, nausea, and focal neurological symptoms (hemiparesis, sensory motor aphasia, adverse epileptic seizures, paresthesias) with rapid onset of remission. Despite the fact that meningeal signs were absent all the time of observation, lymphocytic pleocytosis and cellular-protein dissociation of the cerebrospinal fluid allowed us to diagnose benign recurrent lymphocytic meningitis. In this clinical case, the study of cerebrospinal fluid by the method of polymerase chain reaction showed no DNA-containing herpes viruses. IgG antibodies to herpes simplex virus, cytomegalovirus and Epstein-Barr virus revealed by enzyme immunoassay allowed to confirm the latent herpetic mixed infection in a patient.

The rare occurrence of benign recurrent lymphocytic meningitis, lack of awareness of doctors make it difficult to diagnose and lead to a late start of treatment. It is necessary to routinely apply modern methods of molecular genetic diagnosis, and develop clinical guidelines for the diagnosis and treatment of this disease.

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