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A case report of benign recurrent aseptic meningitis and literature review

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Abstract

Benign recurrent meningitis, also known as Mollaret's meningitis (MM), is characterized by recurrent headache, fever, meningeal irritation and sterility of cerebrospinal fluid examination, which is rare in clinic. Although with clear diagnostic criteria, there are still many unclear aspects of its pathogenesis, and treatment of this disease. The author reported a case of benign recurrent aseptic meningitis, who had three episodes of acute headache with or without fever. The patient was treated with ceftriaxone, acyclovir and cefazoxime for the first time, cefazoxime, cefimidazole and mebendazole for the second time, and piperacillin and acyclovir for the third time. The results showed that the patient did not recover completely in the first two times and fully recovered at the third time. Based on the current research, the author believes that for MM, mainly symptomatic relief, indomethacin should be recommended, and too much antiviral treatment is not needed.

Keywords: meningitis; aseptic; Mollaret's meningitis (MM); gene sequencing.

Practical Application: Benign recurrent meningitis, also known as Mollaret's meningitis (MM), is characterized by recurrent headache, fever, meningeal irritation and sterility of cerebrospinal fluid examination. We reported a case of benign recurrent aseptic meningitis, who had three episodes of acute headache with or without fever. The patient was treated with antibiotics. The results showed that the patient did not recover completely in the first two times and fully recovered at the third time. In conclusion, we believe that for MM, mainly symptomatic relief, indomethacin should be recommended, and too much antiviral treatment is not needed.

1 Introduction

Benign recurrent aseptic meningitis, also known as Mollaret's meningitis (MM) is a very rare neurological disease. Pierre Mollaret, first described recurrent episodes of aseptic meningitis in three patients in 1944 (La, 1944). Bruyn et al. (1962) proposed diagnostic criteria for MM, including recurrent episodes of severe headache, meningismus and fever, spontaneous remission of symptoms and signs, CSF pleocytosis with large endothelial cells, neutrophils, and lymphocytes, and no identified causative etiological agent. Although with clear diagnostic criteria, there are still many unclear aspects of its pathogenesis, and treatment of this disease. We reported a case of MM and reviewed the literature in order to improve the understanding of the diagnosis and treatment.

2 Clinical data

A 33-year-old male patient was admitted to hospital for acute headache with or without fever at 10/03/2018, 01/18/2019 and 02/24/2020, respectively. There was no history of genital herpes infection in the medical history. Meningeal irritation sign was positive by physical examination. After lumbar puncture, white blood cells were found to be elevated by 40~168*10^6/L. MRV showed that the venous sinus was smaller in the right than that in the left (Figure 1). The patient was treated with ceftriaxone, acyclovir and cefazoxime for the first time, cefazoxime, cefimidazole and mebendazole for the second time, and piperacillin and acyclovir for the third time. The symptoms disappeared completely in about one week after each treatment. The cerebrospinal fluid of lumbar puncture was reexamined on the 8, 27 and 12 days after onset, respectively. The results showed that the patient did not recover completely in the first two times and fully recovered at the third time. The results of six cerebrospinal fluid were shown in Table 1. The fifth cerebrospinal fluid was examined by cell staining, but no cells were found due to limited number. No bacteria were found in cerebrospinal fluid after repeated examination. TORCH test (Table 2) was completed each time, which showed that there was no basis for new herpes simplex virus (HSV) infection with HSVIgG (+) and HSVIgM (-). For the fifth time, a full set of pathogenic microbiological macro gene detection (including DNA and RNA detection) in cerebrospinal fluid was carried out, and no basis for pathogenic microorganisms was found. Human herpesvirus 7 (HHV-7), Epstein-Barrvirus (EBV) and Enterobacter Higuchi were found only in the suspected background, but they all had only one sequence, so benign recurrent meningitis (Mollaret's meningitis, MM) was considered.

3 Discussion

Pierre Mollaret, first described three patients with benign recurrent endotheliocytic meningitis with recurrent episodes

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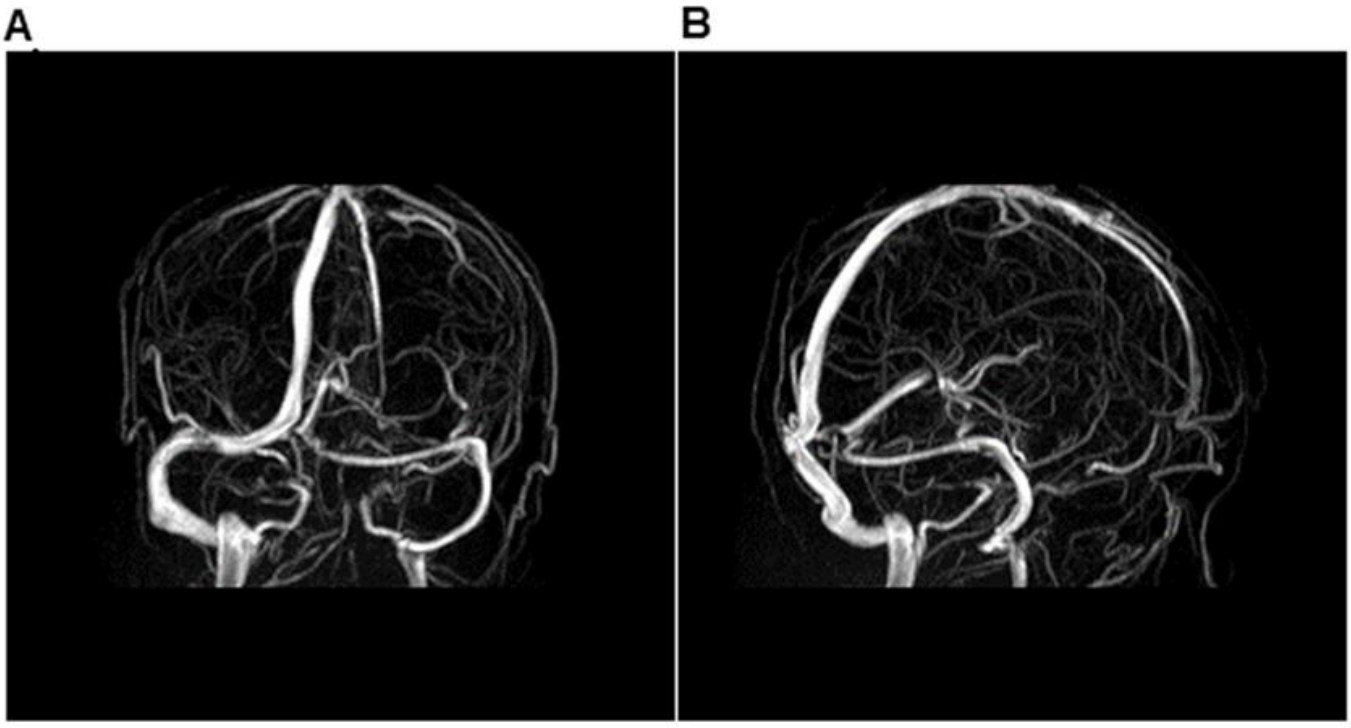

Figure 1. MRV showed that the venous sinus was smaller in the right than that in the left. (A) Frontal image; (B) Side view.

Table 1. Comparison of six cerebrospinal fluid examinations.

Measures	2018/10/13	2018/10/21	2019/1/12	2019/2/8	2020/2/24	2020/3/7
Pressure	145	80	130	90	160	155
WBC	40	20	90	9	168	0
Monocyte ratio	100%	-	95%		98%	0
RBC	0	15	1	-	15	0
Multinucleated cells	0	0	5	-	2	0
Protein	23.9	24	49.8	20.6	56.9	22.1
Chlorine	125.9	121.4	122.9	127	123.1	127.3
Glucose	3.7	3.2	2.6	3.2	3.7	3.5
ADA	0.2	1.2	0.6	0.4	0.1	1.1
LDH	15	16	14	14	20	11

WBC, white blood cells; RBC, red blood cells; ADA, adenosine deaminase activity; LDH, lactate dehydrogenase.

Table 2. Comparison of three TORCH examinations.

TORCH	2018/10/3	2019/1/18	2020/2/24	2020/2/24
ToxIgG (IU/mL)	-	-	-	<3.0
ToxIgM (AU/mL)	-	-	-	<3.0
RubIgG (AU/mL)	+	+	+	75.3
RubIgM (AU/mL)	-	-	-	<10
CMVIgG (IU/mL)	+	+	+	97.6
CMVIgM (AU/mL)	-	-	-	<5
HSVIgG	+	+	+	4.25
HSVIgM	-	-	-	<0.5

of aseptic meningitis, characterized by transient fever headache and vomiting in 1944 (La, 1944). Steel et al. (1982) was the first to isolate herpes simplex virus-1 (HSV-1) from cerebrospinal fluid of patients with MM in 1981. However, it was not until the application of polymerase chain reaction (PCR) technology that there was a breakthrough. In 1991, Yamamoto et al. (1991) reported for the first time that a case of MM was caused by herpes simplex virus (HSV). Evidence showed that HSV-2 was the most common cause of MM, accounting for about 81.16% of all cases, which is consistent with previous reports (Benchetrit et al., 2019). Except for HSV, there were reports of MM caused by other virus infection, including varicella zoster virus (VZV), (Gluck et al., 2019; Gadhiya & Nookala, 2020) West Nile virus (Gluck et al., 2019), EB (Gadhiya & Nookala, 2020), human herpesvirus-6 (HHV-6) (Gadhiya & Nookala, 2020), influenza virus (Shah et al., 2014), and enterovirus (EV) (Kumar et al., 2016). Furthermore, there were some other potential etiologies, including 1) brain and spinal epidermoid cysts, 2) sarcoidosis, 3) systemic lupus erythematosus, 4) Behcet's disease, 5) Sjögren's syndrome, 6) drug-induced, e.g. non-steroidal anti-inflammatory drugs,

7) Monoclonal antibody Tocilizumab (TCZ) (Benchetrit et al., 2019; Kumar et al., 2016; Lee & Lee, 2019; Chu & Eustace, 2018; Richebé et al., 2018).

Willmann et al. (2010) proposed the deficiency of immune system in patients with MM. Toll-like receptor 3 (TLR-3) trigger is thought to induce innate immune response by stimulating interferon production and activating a variety of cytokines and chemokines. And lack of TLR-3 trigger may lead to recurrent meningitis. Kawabori et al. (2019) found that cytokines, especially cytokines in cerebrospinal fluid, such as IL-6 and TNF-a, increased significantly during meningitis. Not only TLR-3, but also many other factors may be involved in the development of the disease. Kawamoto et al. (2018) believed that glycosylphosphatidylinositol (GPI) anchoring protein deficiency mutation was a new pathogenesis of recurrent meningitis with unknown etiology. The loss of these proteins leaded to over-activation of supplement and reactive symptoms, including recurrent meningitis (Serafini et al., 2020; Santos et al., 2020; Bakkaloglu et al., 2021).

There was no significant difference between clinical manifestations and meningitis of other causes, with headache, fever and meningeal irritation as the main manifestations. However, there were also some untypical manifestations. Dobkin found that aseptic meningitis could cause secondary migraine, and Gadhiya & Nookala (2020) found cases of chronic intractable migraine with optic papilla edema (Dobkin, 1981). Clinical symptoms are usually lasting for 3~5 days, and can be completely relieved for 5~7 days (Kumar et al., 2016; Bhuiyan et al., 2017). The attack intervals varies from weeks to months and the longest recording interval is 28 years (Kumar et al., 2016; Shalabi & Whitley, 2006). The median number of attacks is 3~8 times (Benchetrit et al., 2019), with highest number of 121 times (Kawamoto et al., 2018; Poulikakos et al., 2010). Bhuiyan et al. (2017) believed that with the passage of time, the frequency of recurrence would be reduced. Cerebrospinal fluid examination is characterized by elevated leukocytes, ranging from several to hundreds, half no more than 300/mL (Lee & Lee, 2019) and also reported with extremes (Gluck et al., 2019; Kawamoto et al., 2018). The cerebrospinal fluid pressure was normal or slightly increased, and the highest report was 370 mmH_2O at present (Gadhiya & Nookala, 2020). In addition, lymphocytes were dominant, protein was slightly increased, the ratio of glucose to chloride was normal (Yoganathan et al., 2017). Mollaret cells may be found in some patients during the first 24 hours, which are formed when monocytes are invaded by the virus (Rigi et al., 2015). In addition, cerebrospinal fluid analysis showed an increase in IgG index and constant oligoclonal bands in some cases (Gadhiya & Nookala, 2020).

Bruyn et al. (1962) determined the diagnostic criteria of MM in 1962. But with the development of etiology, there is a tendency to make etiological diagnosis for those who can find the cause. For example, the relevant virus "recurrent viral meningitis", and the term "MM" should be limited to idiopathic recurrent aseptic meningitis (Wright et al., 2019). As for etiological diagnosis, at present, it mainly aimed at the detection of possible pathogenic microorganisms. The gold standard is PCR test (NDA+RNA) of cerebrospinal fluid. Among them, the sensitivity of HSV-DNA is 95% and the specificity is 100%. HSV-DNA is the most sensitive when sampling 5 days after the onset of symptoms, although HSV-DNA does not always appear in recurrent attacks, which may be related to the lower viral load and subsequent sample collection time (Bhuiyan et al., 2017). In other words, although no virus was found in this case, it was not completely ruled out that it was caused by virus infection. It should be noted that other previously mentioned causes such as epidermoid cyst, connective tissue disease, and related drug factors still need to be screened.

There are no clear treatment recommendations in acute period due to the rarity and benign course of the disease (Poulikakos et al., 2010). Although the antiviral treatment may be effective to more than 80% of the disease, there are no randomized controlled trials to verify the efficacy due to the small number of cases. It is uncertain whether MM can be self-relieved with no use of medication. It has been reported that anti-C5 antibody (Eculizumab Injection) is effective against PIGT mutation. Most patients may only need symptomatic treatment (Kawamoto et al., 2018). For example, indomethacin is estimated to inhibit periodic abnormalities of eicosenoic acid in the brain, leading to fever reduction and subsequent inflammation (Kawabori et al., 2019). Others such as steroids, colchicine and antihistamines, and butylamine were not found to be helpful (Shalabi & Whitley, 2006). In addition, there is no conclusion as to whether long-term medication is needed, and there is no recommendation as to whether preventive treatment is needed. The case showed that recurrent HSV-2 genital ulcer was associated with recurrent meningitis, and daily chronic inhibition of acyclovir 800 mg significantly improved (Abou-Foul et al., 2014). However, in a recent prospective, randomized, double-blind, placebo-controlled, multicenter trial in Sweden in 2012, more than 100 patients with primary or recurrent HSV-2 meningitis did not find antiviral inhibitory therapy (valaciclovir) was effective for the prevention of recurrent meningitis (Aurelius et al., 2012). However, many experts recommended the use of inhibitory therapy (Shalabi & Whitley, 2006). Other drugs such as a case of recurrent aseptic lymphocytic meningitis were documented in familial Mediterranean fever and responded to prophylactic colchicine treatment (Gadhiya & Nookala, 2020). However, there is no sufficient evidence to show that MM hormone, colchicine, phenylbutyrazone, antihistamines and so on can prevent recurrence (Shalabi & Whitley, 2006).

4 Conclusion

MM, a rare clinical benign meningitis without recurrent manifestation, was mainly caused by HSV-2, with the progress of PCR technology, even if one or more PCR tests fail to detect the pathogen. Based on the current research, the author believes that for this disease, mainly symptomatic relief, indomethacin should be recommended, and too much antiviral treatment is not needed.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and

with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.This study is approved by the Ethics Committee of Zigong first people's Hospital. Written informed consent was obtained.

Conflict of interest

None.

Availability of data and material

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

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