

## A Case of Mollarets Meningitis In Apollo Hospitals Dhaka

Bhuiyan AA<sup>1</sup>, Rahman KM<sup>2</sup>, Alam MJ<sup>3</sup>

---

### Abstract

Mollarets Meningitis is defined as a benign recurrent aseptic meningitis characterized by more than three episodes of fever, headache, meningeal irritation lasting typically 3-5 days. It has spontaneous recovery without any residual neurological deficit. Mollaret in 1944 described this extremely rare form of self-limiting aseptic recurrent benign meningitis. Here we present the report of a patient with Mollarets Meningitis with some atypical features. Early diagnosis may prevent prolonged hospital admissions, unnecessary investigations, and exposure to unnecessary medications, with their associated considerable costs.

### Keywords

Mollarets Meningitis, Recurrent Benign Lymphocytic Meningitis, Herpes simplex type 2 virus

### Introduction

Mollaret meningitis is a rare form of meningitis that is recurrent, aseptic, mild, and self-limiting. When initially described by Mollaret, this form of aseptic meningitis had no identifiable infecting agent.<sup>1</sup> New sophisticated diagnostic tools have now identified Herpes simplex type 2 virus as the most commonly isolated agent.<sup>2</sup> The case presented in this article is of a patient with a history of frequent bouts of recurrent aseptic meningitis spanning a period of 2 years.

Spinal taps performed on her during her previous hospitalizations for meningitis indicated no known specific infectious cause.

### Case Report

A 66 years old right handed female was admitted to Apollo Hospitals Dhaka with sudden onset of

headache, confusion, irrelevant talk and behavioral disturbance since morning of 04/01/2017. She had associated dry cough, sore throat, redness of the eye, generalized body ache 3-4 days prior to these symptoms. She had no fever, neck stiffness, vesicular eruptions on her lips, arthralgia, skin rashes, gastro-intestinal upset. She had no history of genital herpes, recent travel or insect bite. There were no H/O similar symptoms in the family members.

She was admitted to AHD on 05/10/16 with 1-day H/O fever, headache, confusion, irrelevant talk, behavioral disturbance. Routine investigations were only significant for ESR = 47, CRP = 1.16 (normal up to 0.33). CT scan of the brain was normal.

She was treated with I/V ceftriaxone (2 gm - 12 hourly) and I/V Acyclovir for 10 days (10 mg/kg 8 hourly). She showed significant resolution of

1. Sr. Consultant & Coordinator, Dept. of Neurology, Apollo Hospitals Dhaka. 2. Sr. Consultant, Dept. of Neurology, Apollo Hospitals Dhaka. 3. Sr. Medical Transcriptionist, Dept. of Neurology, Apollo Hospitals Dhaka.

her symptoms from 4th day.

She also had two other episodes in last 2 years with similar symptoms. Last attack occurred 1 year ago. She was treated in a local Hospital.

On examination, her vitals were found as follows: Pulse: 106/minute, regular, BP: 110/70 mmHg, temperature: 99.4°F, respiratory rate: 16/minute, SpO2: 100 % on room air.

Neuro examination showed patient was restless and confused. She was responding inappropriately to simple questions and her speech was slurred. Cranial nerves, motor, sensory and reflexes showed no abnormality. Neck stiffness was present.

Eyes was congested without any skin rashes, lymphadenopathy or organomegaly. Other

systemic examination was unremarkable.

Patient had H/O hypertension, ischemic heart disease, coronary stenting, recurrent respiratory tract infection and UTI. Past surgical history was significant for surgery of small intestine for carcinoid tumor in 2008 and surgery for nephrolithiasis.

She has no H/O alcohol intake, smoking, recreational drug use. She is a retired famous film actress of 60's and 70's.

**Investigations:**

CBC, ESR, Electrolytes, CRP, LFT was normal. S. ANA was negative. Serum Herpes 1 and 2 was negative (Serum / Throat).

Drug abuse profile -unremarkable. MRI of Brain – Normal. CT scan of PNS: sinusitis.

**Table I: Results of CSF studies on 2 occasions**

Date	Protein	Glucose	Cell Count	Combined Bacterial Antigen	PCR for Viral Marker	PCR for TB
04.01.2017	71 mg/dl	63 mg/dl	75 cells/mm <sup>3</sup> (Neutrophil 95%)	Negative	Negative	Negative
05.10.2016	106 mg/dl	73.8 mg/dl	115 cells/mm <sup>3</sup> (Neutrophil 99%)	Negative	Negative	Negative

She was treated with I/V Acyclovir 10 mg/kg 8 hourly for 8 days and I/V Ceftriaxone was discontinued after 3 days. She had complete recovery without any deficit. She was discharged home with oral Acyclovir.

**Discussion**

Recurrent Benign Lymphocytic Meningitis

(RBLM) is a rare illness that manifests as a benign, recurrent form of aseptic meningitis and is characterized by as few as 3 to at least 10 episodes of fever and meningism lasting 2–5 days, followed by spontaneous recovery.<sup>1,3</sup> There is significant patient-to-patient variability regarding the time to recurrence; it may vary from weeks to months or even years. Over time,

recurrences become less common, although data from prospective studies that support this opinion are limited. Indeed, some studies suggest that patients who have <3 episodes of meningitis should not receive a diagnosis of RBLM.<sup>4</sup>

The patient described in our case report was an elderly lady had four episodes of fever, headache, confusion and behavioral disturbance lasting 3-5 days with complete resolution of symptoms without any residual neurological deficit. She had the episode mostly associated with sore throat. CSF examination in the 2 episodes recorded in AHD showed mild protein elevation, normal glucose level, neutrophilic leukocytosis with negative PCR for viruses (including Herpes) and TB. CT scan and MRI of the Brain was normal. Serology for Herpes virus 1 and 2 was negative.

This patient fulfilled the criteria proposed by Bruyn et al<sup>6</sup> for the clinical diagnosis: recurrent attacks separated by being symptom-free weeks or months, spontaneous remission of symptoms and signs, recurrent episodes of severe headache, meningismus, and fever. Clinical and pathologic evidence of infectious meningitis were absent.

As shown in earlier multiple studies patient is a female, where it is more common.

She had 4 attacks in the last two years of similar symptoms with complete resolution of symptoms in 3-5 days without any residual neurological deficit. CSF studies was unusual as it was showing neutrophilic leukocytosis and was PCR negative for Herpes 1 and 2 viruses.

Patients with RBLM present with acute onset of

headache that can be severe, as well as fever, photophobia, and meningism. The episodes are painful but self-limited. Signs and symptoms reach maximum intensity within a few hours of onset. Each episode typically lasts 1–3 days, but one report recorded persistence of symptoms for 3 weeks with subsequent recurrences every few weeks.<sup>5</sup>

Approximately one-half of patients have transient neurological manifestations, including seizures, hallucinations, diplopia, cranial nerve palsies, or altered levels of consciousness. These symptoms are transient and, if they persist, a diagnosis of RBLM should be excluded.

Several findings are obvious from different reviews. There was a predominance of females (female to male ratio= 26:15), the mean age of the patients was approximately 35 years, and the number of episodes ranged from 3 to 8.<sup>4,6,7</sup>

From the available case reports, we determined that RBLM is most frequently caused by HSV-2 and much less frequently by HSV-1.<sup>4,8</sup>

Other viruses, such as Epstein-Barr virus, coxsackievirus and echoviruses, have been implicated as causes of recurrent meningitis; however, data to support this condition have not been rigorously collected.<sup>3</sup> Not all patients have an established pathogenesis. HSV-1 usually colonizes the trigeminal ganglia during the latent period, but it can be found in other dorsal root ganglia, as well. In contrast, HSV-2 usually colonizes the sacral sensory ganglia during the latent period.<sup>9,10</sup> The reactivation of HSV-1 results in herpes labialis or, less frequently, in stomatitis, keratoconjunctivitis or genital herpes. The reac-

The reactivation of latent HSV-2 results in recurrent genital herpes. For both viruses, reactivation is more frequently associated with asymptomatic infection and viral shedding in the absence of symptoms. The predominant, characteristic CSF abnormality is a lymphocytic pleocytosis. Some investigators have proposed that RBLM is different from Mollaret meningitis, because the former tends to cause initial CSF lymphocytic predominance, and the latter causes initial polymorphonuclear pleocytosis followed by lymphocytic predominance.<sup>4</sup>

The appearance of large granular plasma cells is considered to be the hallmark of Mollaret meningitis.<sup>7</sup>

These cells can be demonstrated by Papanicolaou's stain and are usually evident during the first 24 h of the illness, but then they disappear quickly.

They may also be absent in CSF. Protein levels in CSF are mildly elevated, and the glucose level is usually normal. The CSF cell count and results of blood chemistry tests are comparable to those associated with other aseptic meningitides with a lymphocytic predominance.<sup>4</sup>

Analysis of CSF by PCR for HSV DNA is considered to be the gold standard for diagnosis. However, other etiologies should additionally be sought at the time of initial patient evaluation. In the study by Tedder et al.<sup>4</sup>, 85% of the patients had a result positive for HSV DNA by PCR of their CSF sample. One patient had HSV-1 infection, and 10 patients had HSV-2 infection.

The presence of the HSV antibodies in CSF does not confirm the diagnosis, because the blood-brain barrier may be inflamed, which allows HSV antibodies to penetrate the CSF. Culture of the CSF for HSV is usually and not surprisingly negative.<sup>11, 12</sup>

Historically, acyclovir has been used for treatment and suppression of HSV infection.<sup>12-14</sup> RBLM is a benign, self-limited illness; however, acyclovir has been administered as therapeutic treatment, as well as for the suppression of recurrences. Some investigators do not think acyclovir therapy alters the natural course of the illness.<sup>14</sup> Administration of intravenous acyclovir (5–10 mg/kg every 8 hours for 7–10 days) has putatively resulted in rapid resolution of infection. More recently, because of improved pharmacokinetics, second - generation anti-herpetic drugs - valacyclovir and famciclovir - have been shown to be efficacious for the management of genital herpes.

Both medications have been used to treat patients with RBLM and, as noted below, to provide long-term suppressive management of infection.

As would be expected, episodic therapy would not likely influence subsequent recurrences. Regardless of the medical history of those individuals with a diagnosis of HSV-2 RBLM who have been proven to have the illness, counseling about genital herpes and the possibility of transmission of infection should be a component of treatment.

### Conclusion

Mollaret syndrome, although rare, should be considered in all persons with recurrent aseptic meningitis. It can be diagnosed by PCR analysis of spinal fluid for the presence of viruses, in particular Herpes simplex type 2.

The sensitivity of this test is 95% and specificity is 100%. Diagnosis can be made by detecting HSV-2 DNA in CSF by PCR with sensitivity and specificity of 95% and 100%, respectively.<sup>9</sup> In all confirmed cases of HSV-2 Mollaret's meningitis, counseling on genital herpes and the possibility of transmission of infection should be a component of the treatment. Treatment with acyclovir may be beneficial in decreasing the severity and duration of attacks and in preventing further episodes. The sensitivity of this test is 95% and specificity is 100%. Diagnosis can be made by detecting HSV-2 DNA in CSF by PCR with sensitivity and specificity of 95% and 100%, respectively.<sup>9</sup> In all confirmed cases of HSV-2 Mollaret's meningitis, counseling on genital herpes and the possibility of transmission of infection should be a component of the treatment. Treatment with acyclovir may be beneficial in decreasing the severity and duration of attacks and in preventing further episodes.

### References

1. Mollaret P. La méningiteendothélio- leucocytaire multi-récurrentebénigne. *Rev Neurol (Paris)*, 1944; 76:57-67
2. Mollaret's meningitis Available at: <http://www.whonamedit.com/synd.cfm/1537.html>. Accessed 18 September 2006
3. Galdi AP. Benign recurrent aseptic meningitis (Mollaret's meningitis): case report and clinical review. *Arch Neurol*, 1979; 36:657-8
4. Tedder DG, Ashley R, Tyler KL andLevin MJ. Herpes simplex virus infection as a cause of benign recurrent lymphocytic meningitis. *Ann Intern Med*, 1994; 121:334-8
5. King JW., Mollaret's meningitisAvailable at: <http://www.ccm.lsuhs-c.edu/bugbytes/Volume4/BB-v4n3.html>. Accessed 18 September 2006
6. Kupila L, Vainionpaa R, Vuorinen T, Marttila RJ andKotilainen P. Recurrent lymphocytic meningitis: the role of herpesviruses. *Arch Neurol*, 2004; 61:1553-7
7. Chan TY, Parwani AV, Levi AW andAli SZ. Mollaret's meningitis: cytopathologic analysis of fourteen cases. *DiagnCytopathol*, 2003; 28:227-31
8. Picard FJ, DekabanGA, SilvaJ and Rice GP. Mollaret's meningitis associated with herpes simplex type 2 infection. *Neurology*, 1993; 43:1722-7
9. Plummer G. Isolation of herpesviruses from trigeminal ganglia of man, monkeys, and cats. *J Infect Dis*, 1973; 128:345-7
10. Warren KG, Devlin M, Gilden DH, Wroblewska Z, Brown SM, Subak-Sharpe J, et al. Isolation of herpes simplex virus from human trigeminal ganglia, including ganglia from one patient with multiple sclerosis. *Lancet*, 1977; 2:637-9
11. Lafferty WE, Coombs RW, Benedetti J and Critchlow C, Corey L. Recurrences after oral and genital herpes simplex virus infection: influence of site of infection and viral type. *N Engl J Med*, 1987; 316:1444-9
12. Whitley RJ, Lakeman F. Herpes simplex virus infections of the central nervous system: therapeutic and diagnostic considerations. *Clin Infect Dis*, 1995; 20:414-20
13. Townsend G, Scheld W. Infections of the central nervous system. *Adv Intern Med*, 1998; 43:403-47
14. Bergstrom T, Alestig K. Treatment of primary and recurrent herpes simplex virus type 2 induced meningitis with acyclovir. *Scand J Infect Dis*, 1990; 22:239-40