

# Mollaret's Meningitis In Association With Herpes Simplex Virus Type 2

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## Abstract

Benign recurrent aseptic meningitis, also called Mollaret's meningitis, is a rare, albeit well described disease. The exact etiology is unknown though Herpes Simplex Virus is now thought to be the most likely pathogen. We report a case of a 41-year old woman who experienced three episodes of aseptic meningitis with lymphocytic pleocytosis. In the third episode Herpes Simplex Virus type 2 DNA was detected in the CSF by PCR. This suggests that Herpes Simplex Virus should be sought for in in-patients presenting with recurrent episodes of aseptic meningitis.

## CASE REPORT

A 41-year-old Brazilian woman presented with a two-day history of severe headache, neck stiffness and generalized muscle aches. She was seen in the emergency room a day prior to her admission to the hospital, headache was relieved with magnesium sulfate and she was discharged home with advice to follow with her doctor. The next day, she presented to the emergency room with progressively worsening headache. She gave history of neck stiffness and photophobia. She also had associated complaint of nausea. No history of preceding fever, cough or expectoration was elicited. She gave history of 2 prior admissions for similar complaints. The patient was first admitted to a hospital 2 years ago for fever and neck stiffness. A CT brain scan was normal and so was a chest x-ray film. There were no notable abnormalities of the serum electrolytes, chemistry screen or a complete blood count. Lumbar puncture was suggestive of aseptic meningitis. Her symptoms cleared within 24 hours and she was discharged home with a diagnosis of aseptic meningitis.

She was readmitted a year later with similar complaints. The results of her blood tests were unremarkable; lumbar puncture was again suggestive of aseptic meningitis. She was discharged home on the second day.

On her current admission, she had no focal neurological signs apart from nuchal rigidity. Kernig's sign was elicited. Results of CT scan brain, MRI brain, chest x-ray, electroencephalogram, electrocardiogram, blood chemistry,

and complete blood count were all normal. ESR was 7 mm/hr and ANA was negative. The CSF white blood cell count was 114 cells (99% lymphocytes, 1% monocytes). The glucose level was 42 mg/dl with a serum glucose level of 73 mg/dl and the protein level was 71 mg/dl. Gram's stain of the CSF did not show microorganisms and the CSF culture was sterile. CSF VDRL, cryptococcal antigen, Indian Ink and fungal smear were all negative. Mollaret's cells were not seen in the CSF. All symptoms cleared within 48 hours. Subsequently Herpes Simplex Virus (HSV) type 2 DNA was detected in the CSF by PCR amplification indicating the diagnosis of recurrent HSV type 2 meningitis. The patient was treated with intravenous acyclovir sodium (10mg/kg three times a day) for 5 days and was discharged on Valcyclovir prophylaxis (1 gram PO daily) with a diagnosis of Mollaret's meningitis.

## DISCUSSION

Recurrent benign endotheliocytic aseptic meningitis was first described by Mollaret in 1944. Mollaret's meningitis is characterized by repeated episodes of fever (up to 104 °F), meningismus, and severe headache separated by symptom-free intervals of weeks to years. Individual attacks are sudden, with signs and symptoms reaching maximum intensity within a few hours. The initial presentation is clinically indistinguishable from other forms of life-threatening meningitis. During the attacks, Kernig's and Brudzinsky's signs of meningismus are usually present. Headache, neck-pain, generalized muscle aches and neck stiffness usually persist from one to three days but may be

present for up to three weeks. Following a number of recurrences, which can span a period of years, the disease may suddenly disappear. The long-term health of patient seems not to be adversely affected. Transient neurological abnormalities (seizures, diplopia, pathologic reflexes, cranial nerve paresis, hallucinations, and aphasia) have all been reported<sup>2,3</sup>. However persistent neurological deficits should call the diagnosis into question.

CSF obtained early in the course of the illness usually demonstrates large friable "endothelial" cells termed as Mollaret's cells. Mollaret's cells can be demonstrated by the Papanicolaou stain and are now thought to be large activated cells of the monocyte/ macrophage lineage. These cells are thought by many to be the hallmark of Mollaret's meningitis and early on may comprise 60% to 70% of the CSF cells. These cells are usually present for only the first 24 hours and thus can be missed easily if the CSF examination is delayed. After the first 24 hours, the CSF shows a lymphocytic predominance with cell counts usually less than 3000/mm<sup>3</sup>. Low CSF glucose concentration with mild elevation of CSF protein especially the gamma globulin fraction is usually seen.

Recent data suggest that Herpes Simplex Type II and less frequently Herpes Simplex Type I may be etiologic in some if not all cases of Mollaret's meningitis<sup>4,5</sup>. Other etiologic agents that have been considered over the years include trauma and viral infections other than Herpes Simplex<sup>6</sup>. The differential diagnosis thus includes etiologies as varied as Behcet's syndrome, sarcoidosis, Vogt-Koyanagi Harada syndrome, neurenteric cyst of the foramen magnum and ruptured pineal cyst.

Our case presented with signs and symptoms suggestive of viral meningitis. CSF PCR was positive for Herpes Simplex Type II thus confirming the diagnosis of Mollaret's meningitis. The patient had similar episodes of viral meningitis in the past. This suggests that search for Herpes virus DNA by PCR amplification on CSF may be extremely useful in unexplained viral meningitis. This may prevent repeated extensive diagnostic investigations and timely treatment of this infection. A number of intriguing questions are raised by this patient's presentation with regards to the

proper dose and duration of acyclovir needed to ward off future attacks of meningitis. Although no conclusions can be drawn by the case reported here, there are anecdotal reports of repetitive cycles of Mollaret's meningitis ceasing after a short course of acyclovir infusion<sup>2</sup>. Mora et al. reported a case of Mollaret's meningitis that recovered after treatment with colchicine<sup>7</sup>. With respect to prophylaxis with Valcyclovir there are no clear guidelines with respect to dose and duration of therapy. Valcyclovir is approved for prophylaxis against recurrent genital herpes and we suspect it will work in this setting also. Since our patient had 3 episodes of meningitis over a 3-year period each resulting in a brief hospital course or emergency room visit followed by a 2- week absence from work, we opted for the higher 1-gram daily dose though the meningitic episodes may naturally become less frequent with time. Whether these patients require life long prophylaxis to ward off future attacks or a few years of chronic suppressive therapy may suffice remain unanswered. Future studies may offer an answer to these important questions.

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