Case study [chemistry | microbiology]
Recurrent Headache and Febrile Attacks in a Young Woman
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Patient
24-year-old woman.

Chief Complaint
Headache, photophobia, painful and stiff neck, nausea and vomiting (5 to 6 episodes).

Past Medical History
Two years ago, the patient presented twice to the emergency department (ED) over a 2-week period with clinical signs and symptoms suggestive of meningitis. Laboratory investigation of her cerebrospinal fluid (CSF) showed decreased glucose and increased total protein, findings suggestive of bacterial meningitis; however, the CSF cell count was low and no bacterial growth was obtained. Antibiotics were administered and the patient was discharged.

Drug History
No current history of any medications, drugs of abuse, or therapeutic drugs. No other drug history was noted apart from Coproxamol and antibiotics (Augmentin, gentamicin, bezylpenicillin, and chloramphenicol) taken at various times following her earlier admission to the ED.

Physical Examination
The patient was febrile (temperature, 38°C), mildly bradycardic (pulse: 80 bpm), borderline hypertensive (blood pressure, 140/80 mmHg), with neck-stiffness, negative Kernig’s sign (a sign of meningitis in which the patient, in the sitting posture or when lying with the thigh flexed upon the abdomen, cannot completely extend the leg), and no photophobia.

Principal Laboratory Findings

Results of Other Diagnostic Procedures
A computed tomography (CT) scan of the brain was performed and showed a small calcified lesion to the left of the torculax in the posterior fossa which looked like an old lesion (possibly an old granuloma, tuberculous or listerial infection, or a residue of some incident in childhood or infancy) of no current clinical significance. Overall, CT findings on this admission were similar to those obtained during her first presentation to the ED 2 years ago. There was no evidence of hydrocephalus, abscesses, or cysts.

Questions:
1. What is(are) this patient’s most striking laboratory result(s)?
2. How do you explain this patient’s most striking laboratory result(s)?
3. What condition(s) does this patient’s laboratory and other findings suggest?
4. What are the principal complications found in this patient’s condition?
5. What is(are) the most likely cause(s) of the principal complications found in this patient’s condition?
6. Which laboratory and non-laboratory test(s) are appropriate to order on this patient and why?
7. What is the most appropriate treatment for this patient?

Possible Answers:
1. Markedly increased CSF cell count, total protein, albumin, and IgG values; markedly decreased glucose concentration; markedly abnormal CSF indices; and negative tests for bacterial organisms.

2. The markedly increased CSF nucleated cell count (89% polymorphonuclear leukocytes), when coupled with the patient’s presenting signs (meningeal inflammation) and symptoms (headache, recurrent febrile attacks), are suggestive of Mollaret’s meningitis. The increased CSF total protein and decreased glucose concentrations are consistent with a bacterial meningitis; however, microbiological analysis failed to isolate or identify a causative organism. Moreover, the CSF total protein concentration was markedly higher than that
normally seen in patients with bacterial meningitis, while this patient’s values for all CSF indices were considerably higher than those observed typically in patients with multiple sclerosis (MS). In addition, this patient’s CSF electrophoresis pattern did not demonstrate the presence of oligoclonal bands (o-bands) in the gamma-region. In active disease, o-bands are present on electrophoresis of CSF from 95% of MS cases.1

Diagnosing central nervous system (CNS) infection relies heavily on biochemical and microbiological analyses of CSF. Although microbiological identification of an infectious bacterial organism from the culture of CSF from a patient with signs and symptoms suggestive of meningitis provides a definitive diagnosis of bacterial meningitis, most clinical chemistry laboratories also provides measurements of CSF glucose and total protein concentrations, although results for these tests are not always conclusive. More than 80% of CSF protein originates from plasma by ultrafiltration of low molecular weight proteins through the walls of the capillaries in the meninges and choroid plexus. The remainder originates from intrathecal synthesis. Bacterial infection of the meninges normally results in increased CSF total protein levels due to altered permeability of the blood-brain barrier (BBB) and/or increased intrathecal synthesis of immunoglobulins by activated lymphocytes and/or bacterial proteins from increased growth of bacteria within the meninges and CSF. Because bacteria metabolize glucose for energy, a decreased CSF glucose concentration is suggestive of bacterial infection; however, other non-inflammatory conditions such as a neoplasm can also cause reduced CSF glucose levels. In cases of viral infection or autoimmune encephalitis, glucose levels will remain within the reference range whereas total protein is typically elevated. The negative microbiology findings in our patient may be explained by the patient’s broad-spectrum antibiotic treatment. Moreover, the fact that the patient’s condition improved over time, concomitant with a decrease in her CSF total protein and an increase in her CSF glucose levels, during antibiotic treatment provides additional evidence in support of bacterial meningitis as the cause of this patient’s signs, symptoms, and laboratory findings. Lastly, the similarity between serum and CSF values for the Alb/IgG ratio and the markedly increased Alb index suggest further that changes in the permeability of the blood-brain barrier (BBB) are the most likely cause of her markedly increased CSF IgG concentration rather than intrathecal production of IgG, a characteristic finding in patients with MS. The Alb Index is a sensitive indicator of abnormalities in the permeability of the BBB.

### 3. Most likely diagnosis: Mollaret’s meningitis

This is a rare cause of recurrent aseptic meningitis characterized by numerous febrile episodes that may occur over many years.
with symptom-free intervals ranging from weeks to years. The condition was described in 1944 and is associated with the presence of epithelial and/or endothelial cells in the CSF. Although Mollaret suspected that the disease symptoms were of viral origin, no viral agent has ever been found. In our patient, 2 prior recurrent febrile episodes occurred over a 2-week period, and this third episode (2 years later) was associated with similar presenting signs and symptoms and biochemical findings except for a much higher CSF total protein concentration in the recent episode. In all episodes, biochemical analysis of CSF showed decreased CSF glucose and increased total protein—a finding suggestive of bacterial meningitis, despite the negative microbiology findings. The failure to show bacterial growth in her CSF during her prior episodes was due most likely to the antibiotic treatment, prescribed by her general practitioner (GP), 1 week prior to her admission to the ED. A week later, her symptoms recurred and her CSF demonstrated a cell count of 300 nucleated cells/µL, a glucose concentration of less than 18 mg/dL, and a total protein concentration of 650 mg/dL.

Several cases of aseptic meningitis have been reported previously. Brunel and colleagues reported a case of a child with 5 episodes of unexplained aseptic neutrophilic meningitis, later attributed to an intracranial epidermoid cyst. Schwartz and Ballentine described a case of a child who presented 10 times with recurrent aseptic meningitis and an intracranial epidermoid tumor was found at autopsy. Becker and deChadarevian described a female who presented at age 6 years with aseptic neutrophilic meningitis and subsequently had 17 febrile episodes over a 42-month period. Although this patient’s cranial CT scans were negative on 2 occasions, a subsequent scan revealed the presence of an epidermoid cyst in the posterior fossa. In 1990, Crossley and Dismukes described the case of a 32-year-old man who presented initially in 1972, and during a 14-year period was hospitalized 30 times for recurrent attacks of aseptic meningitis which occurred more frequently during the most recent 4-year period. The mean interval between episodes in the first 9 years was about 237 ± 68 days, while the mean interval during the last 4 years was 97 ± 40 days. Two cranial CT scans during this patient’s episodes of meningitis were negative; however, examination of his CSF revealed the presence, on several occasions, of large mononuclear cells originally described by Mollaret as endothelial cells. However, subsequent ultrastructural and immunocytochemical studies indicated a monocyte/macrophage lineage for these cells. Thirteen years later, this patient’s cranial CT scan revealed the presence of a 2.2 cm mass in the posterior fossa, which proved to be an avascular, well encapsulated cyst that was surgically resected. In the 2 years following excision of the cyst, the patient had no further episodes of meningitis. Cranial CT scans may be negative in patients with Mollaret’s meningitis if the CT scan is obtained during episodes of acute meningitis when epidermoid cysts may be empty or very small following extravasation of the cyst fluid into the CSF. It has been suggested that the use of contrast-enhanced CT or nuclear magnetic resonance imaging (MRI) during asymptomatic intervals is useful in visualizing the presence of a cranial cyst(s).6

4. The principal complications of meningitis include neuropathy with possible neurological deficit. There is no specific treatment protocol for these patients; however, patients are treated typically with broad-spectrum antibiotics and observed closely. Data on long-term follow-up of these patients are not available in the literature. Our patient had 3 recurrent episodes of aseptic meningitis over a 2-year period and will need to be closely monitored.

5. The cause(s) of Mollaret’s meningitis, including the etiology of the neurological deficit associated with this disease, are currently unknown.

6. Cerebrospinal fluid electrophoresis and serum interleukin-6 (IL-6) levels. Protein electrophoresis of CSF from patients with meningitis may be useful because in patients with meningitis there is inflammation of the meningeal membrane that leads to increased permeability of the BBB and the leakage of plasma proteins into the CSF. Thus, in these patients, the CSF protein electrophoretic pattern is similar to that of serum. In addition, an increased globulin band may also be observed, indicative of increased CSF intrathecal immunoglobulin synthesis. This patient’s markedly increased CSF IgG synthesis rate and IgG loc value are consistent with increased intrathecal IgG synthesis, while the markedly increased Alb index is consistent with significant increased permeability of the BBB [T1]. Measurement of CSF IL-6 levels may be useful in evaluating patients with meningitis because IL-6 is a useful marker of inflammation. We have shown that elevated CSF IL-6 levels occur in patients with bacterial meningitis but not in those without meningitis or with viral or aseptic meningitis. Despite our patient’s increased CSF total protein, suggestive of bacterial meningitis, her CSF IL-6 level was not elevated, lending further support to the diagnosis of aseptic meningitis.

7. There is no known cure for this condition. Patients with Mollaret’s meningitis are treated typically with broad spectrum antibiotic therapy and conservative follow-up. Both colchicine and indomethacin have been reported to relieve the symptoms of this disease.8

**Patient’s Treatment and Course**

The patient was treated with antibiotics, recovered well, and was discharged to follow-up over the next few months.

**Keywords:** cerebrospinal fluid, Mollaret’s meningitis, CSF indices


