Sarcoid Meningitis With Fulminant Delirium and Markedly Abnormal Cerebrospinal Fluid

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Objective: To describe a patient with an acute fulminant delirium and eventual spinal fluid block secondary to sarcoid meningitis.

Design: Case report.

Setting: Hospital and Neurology Clinic.

Patient: A previously healthy, 24-year-old man.

Interventions: Antimicrobials, corticosteroids, lumbar puncture, myelography, and lymph node biopsy.

Main Outcome Measures: Cerebrospinal fluid, clinical status.

Results: The patient improved after treatment with corticosteroids.

Conclusion: Sarcoid meningitis may present with delirium and spinal block.

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Neurosarcoidosis may affect any part of the nervous system. There is no standard clinical picture. Despite this, we find no existing report of neurosarcoidosis presenting as a fulminant, agitated delirium, nor do we find report of cerebrospinal fluid (CSF) abnormalities as severe as in the patient described herein.1-3

Report of a Case

A previously healthy, 24-year-old man presented to the emergency department reporting chills, diffuse pain, and malaise. After a diagnosis of “viral illness,” he was discharged, taking diphenhydramine hydrochloride as needed (up to 100 mg daily). Abruptly, 3 days after first presentation, he became agitated and incoherent. He returned to the emergency department where his temperature was 98°F, blood pressure was 157/115 mm Hg, and pulse was 65 beats/min. He was hypervigilant, combative, and incoherent. Cranial nerve function, pupillary size, limb strength, coordination, and reflexes were normal. A toxic reaction to diphenhydramine likely contributed but his delirium failed to clear over 2 days despite its discontinuance. His initial agitation responded only partially to 10 mg of intramuscular haloperidol and 10 mg of intravenous lorazepam. Computed tomography (CT) of the head showed no inflammatory lesions, hypodense areas, hydrocephalus, or abnormal contrast enhancement. A preexisting asymptomatic bullet fragment deep in the parietal white matter contraindicated magnetic resonance imaging. Intravenous acyclovir, ceftriaxone sodium, vancomycin hydrochloride, ampicillin, and dexamethasone were used as early therapy.

Initial CSF values included an opening pressure of 55 cm of water, a white blood cell count of 870 × 10³/µL (87% neutrophils, 13% lymphocytes), protein level of 0.206 g/dL, and glucose level of 12 mg/dL (0.67 mmol/L). Early CSF studies did not include a CSF–angiotensin-converting enzyme (ACE) level. Given the initial CSF findings, and positive purified protein derivative test results (15 mm of induration), he began antitubercular therapy of rifampin, isoniazid, pyrimethamine, and ethambutol hydrochloride (RIPE) with 75 mg of oral dexamethasone per day. His mental status normalized over 1 week. Two weeks after initial CSF examination, he underwent repeat lumbar puncture, which showed improvement in the white blood cell count to 112 × 10³/µL (64% neutrophils, 13% lymphocytes). He was subsequently discharged taking RIPE and a tapering dose of steroids.
Table. CSF Findings

<table>
<thead>
<tr>
<th>Weeks After First Presentation</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>5</th>
<th>7</th>
<th>9</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF WBC count, ×10³/µL</td>
<td>870</td>
<td>644</td>
<td>112</td>
<td>1078</td>
<td>810</td>
<td>400</td>
<td>230</td>
<td>440</td>
<td>120</td>
</tr>
<tr>
<td>CSF RBC, ×10³/µL</td>
<td>30000</td>
<td>11000</td>
<td>1000</td>
<td>0</td>
<td>12000</td>
<td>1650000</td>
<td>200000</td>
<td>10000</td>
<td>250000</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>87</td>
<td>89</td>
<td>64</td>
<td>27</td>
<td>38</td>
<td>11</td>
<td>11</td>
<td>32</td>
<td>46</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>13</td>
<td>11</td>
<td>35</td>
<td>72</td>
<td>62</td>
<td>83</td>
<td>46</td>
<td>67</td>
<td>54</td>
</tr>
<tr>
<td>Monocytes, %</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Eosinophils, %</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Protein level, g/dL</td>
<td>0.206</td>
<td>0.319</td>
<td>NA*</td>
<td>0.501</td>
<td>0.378</td>
<td>0.471</td>
<td>0.530</td>
<td>0.738</td>
<td>1.248</td>
</tr>
<tr>
<td>Glucose level, mg/dL</td>
<td>12</td>
<td>18</td>
<td>NA*</td>
<td>27</td>
<td>22</td>
<td>22</td>
<td>32</td>
<td>36</td>
<td>13</td>
</tr>
<tr>
<td>Opening pressure, cm of water</td>
<td>&gt;55</td>
<td>47</td>
<td>50</td>
<td>26</td>
<td>26</td>
<td>26</td>
<td>26</td>
<td>NA†</td>
<td>31</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; NA, not available; RBC, red blood cell; WBC, white blood cell. *Protein and glucose levels not recorded on 1 lumbar puncture. †Opening pressure not recorded on 1 lumbar puncture.

Results of laboratory studies included a negative urine drug screen; normal ACE level (28 U/L [reference range, 9-67 U/L]); normal erythrocyte sedimentation rate; and normal antinuclear antibody, rheumatoid factor, antineutrophil cytoplasmic antibody, lactate dehydrogenase, and Brucella antibody levels. Human immunodeficiency virus test results were negative and a blood T-lymphocyte panel revealed normal absolute counts of CD4+ and CD8+ cells as well as a normal CD4+ :CD8+ ratio. Thick and thin blood smears revealed no parasites, including trypanosomes.

Results of CSF studies were negative and included a Gram stain and culture; fungal culture; cryptococcal antigen test; India ink stain; acid-fast bacilli smear and culture (repeated 5 times); mycobacterial culture; VDRL test; polymerase chain reaction for herpes simplex virus 1 and 2; tests for Epstein-Barr virus, cytomegalovirus, and histoplasma antigen; cytology, flow cytometry for B and T lymphocytes, and Leptomyxidiae ameba antibody test.

During the following 2 months, he developed recurrent episodes of recumbent headache, nausea, neck stiffness, and back pain, each lasting several days. Several of these required readmission to the hospital and repeat CSF analysis. Via bedside lumbar puncture, x-ray myelography, and CT myelography, he underwent a total of 10 CSF examinations. Cerebrospinal fluid values are presented in the Table. Serial CSF analysis revealed lymphocytic pleocytosis up to 1078 white blood cells/mm³ (no longer a neutrophil predominance), a low glucose level (ranging from 13-36 mg/dL [0.72-2.00 mmol/L]), and a markedly high protein level. The CSF ACE level was elevated at 17 U/L (reference range, ≤15 U/L).

Nine weeks after initial presentation, his oral steroid therapy was stopped. One week later, he returned to the clinic reporting new leg weakness. Examination confirmed a muscle strength grade of 4/5 in the proximal leg, impaired gait, and depressed lower extremity reflexes. Electromyography and nerve conduction values supported motor neuronopathy or axonopathy but not myopathy. X-ray myelography showed filling defects in the contrast column over the dorsal aspect of the spinal cord and CT myelography confirmed intradural extramedullary swelling with thickening of the cauda equina, consistent with leptomenigitis and arachnoiditis (Figure 1). At that point, his CSF protein concentration reached a peak of 5.231 g/dL—consistent with complete spinal CSF block.

Ultimately, gallium scintigraphy revealed multiple mediastinal and hilar foci of increased uptake, and CT revealed a 1.7-cm, necrotic-appearing lymph node in the esophageal recess. A biopsy was performed on the lymph node. Histologic examination confirmed noncaseating granulomas of varying ages consistent with sarcoidosis (Figure 2). Fungal and acid-fast bacilli stains were negative. The ratio of CD4 to CD8 cells within the biopsy specimen was 3:1. The patient started taking intravenous steroids (1000 mg of methylprednisolone daily) and then began long-term oral steroid therapy. Within 5 months of presentation, all of his symptoms had abated. He remained normal 9 months after onset but will require long-term immunosuppression.

**COMMENT**

Three features of this case are atypical for neurosarcoidosis: (1) rapid delirium, (2) profoundly inflammatory CSF, and (3) spinal block with a high protein level. Typically, the differential diagnosis of an acute agitated delirium with inflammatory CSF does not include new-onset neurosarcoidosis. Although other authors have described psychosis and agitation in neurosarcoidosis, a rapidly deteriorating diffuse encephalopathy over hours has not been described. Our patient’s initial agitation and delirium were likely caused by a combination of diffuse meningitis, pain from meningeal irritation as well as high intracranial pressure, and a toxic reaction to diphenhydramine, although any proposed mechanism is tentative because there was no imaging or biopsy specimen demonstration of direct central nervous system involvement by sarcoid. Significant encephalitis was unlikely given the lack of focality during his examination and lack of permanent deficits. Acute disseminating encephalomyelitis was considered initially, but over time, it became more improbable because he failed to show abnormalities on repeat contrast-enhanced head CT, he failed to develop focal upper motor neuron signs, and he de-
developed a chronic, recurrent illness. The diagnosis of neurosarcoidosis was based on the gallium study, biopsy findings, and clinical course. The elevated CSF ACE level was only supportive and not confirmatory because the utility of this test is not universally accepted.5,6

The CSF findings in our patient are outside the reported ranges for neurosarcoidosis.7,8 Imaging in our patient was consistent with spinal leptomeningitis, and the high CSF protein level was likely due to secondary CSF block. Spinal fluid block or “loculation syndrome” with a markedly high CSF protein level has historically been termed Froin syndrome from its initial description in 1903.9 Despite the relatively common presentation of neurosarcoidosis with arachnoiditis, or diffuse leptomeningitis, we find no description of sarcoidosis presenting with spinal block and resultant protein elevations to this degree.10 This case reiterates the wide clinical spectrum of neurosarcoidosis and the high index of suspicion required to make an early diagnosis.

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REFERENCES