You're the Flight Surgeon

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You're the flight surgeon at a northern Midwest base during the late summer months working in a small flight medicine clinic. A 43-yr-old male pilot presents to sick call first thing Monday morning complaining of 4 d of dizziness, nausea, and a persistent frontal headache. Additionally, the patient reports a subjective fever that started the day before presenting to the clinic and was accompanied by thirst and the sense of difficulty thinking clearly. Upon questioning, the patient admits to having just returned to the Midwest after a 1-wk vacation to the southern coastal regions of the United States. The dizziness and nausea first started while boating rough seas in the Atlantic with large swells, but the patient assures you that he is an experienced boater who has never been seasick in the past. The patient also mentions briefly a bout of abrupt onset weakness that occurred during the flight home 2 d earlier. On exam the patient is noted to have a temperature of 103.6°F, appears fatigued, weak, and dehydrated, but is responding to questions appropriately and is well oriented. The physical exam is significant for 4/5 strength at all major joints, but absent for nuchal rigidity, and deep tendon reflexes seem suppressed but are present. Stat blood work shows a normal basic metabolic panel, normal hematocrit, and a white blood cell count of $10.6 \times 10^3/mm^3$.

1. Given the clinical picture above, which diagnosis would seem LEAST likely in your differential?

A. Migraine variants.
B. Meningitis (bacterial or viral).
C. Fungal infection.
D. Autoimmune disorder.
E. Drug-induced aseptic meningitis.

ANSWER/DISCUSSION

1. A. Migraine variants. Although migraines can present with a variety of symptoms, including dizziness, weakness, and confusion, and may be preceded by a prodromal phase with thirst and fatigue, the flight surgeon must be cognizant of the "red flag" findings that signal a more insidious problem—headaches associated with a recent head injury, focal neurological signs or symptoms, papilledema, onset of headache syndrome after 50 yr of age, or systemic symptoms such as fever. In this case, the most troubling finding is the fever of 103.6°F, indicating a systemic disease process.

With a presentation of high fever and associated dehydration, progressive fatigue/weakness, and headaches, meningitis should jump to the top of the differential. Drug-induced aseptic meningitis is considered rare and has an unknown incidence, but does present a similar clinical picture. The condition is thought to be caused by one of two methods: direct meningeal irritation by medication or through a type III or IV hypersensitivity reaction. Most commonly associated medications include antimicrobials (e.g., trimethoprim-sulfamethoxazole, cephalexin, metronidazole, amoxicillin, ciprofloxacin, isoniazid). Additional classes of medications associated with drug-induced aseptic meningitis include nonsteroidal anti-inflammatory drugs, immunoglobulins, radiographic agents, and certain vaccines. Autoimmune diseases may also include meningitis as a key neurological complication with all the key findings of bacterial and viral meningitis. The clinical course of meningitis cases related to autoimmune disease can be extremely variable and is thought to be caused by the interaction of disease-specific autoantibodies and cytokines.

The most likely diagnosis includes bacterial, viral, and fungal causes. Acute bacterial meningitis has been defined by the triad of fever, headache, and neck stiffness, but has been shown to be fully present in only 44% of all patients.[6,31] This patient did not present with nuchal rigidity on your exam and you would anticipate a leukocytosis after 4 d of symptoms. Fungal cases of meningitis can present in this manner. Certain fungal infections are endemic to the Midwest (bird and bat droppings can contain histoplasmosis) and coccidiomycosis is found commonly in the San Joaquin Valley of California. Viral infections are the most common causes of meningitis and can be minor infections, frequently referred to as aseptic meningitis, or life threatening as in the case of neuroinvasive disease caused by many viruses in the Enteroviridae and Arboviridae classes.

You decide to start the patient on intravenous fluid replacements and give a 30-mg intravenous dose of Toradol to relieve the headache. Within 60 min the patient clinically appears better and states that he feels much improved. Further discussion with the patient elicits additional historical information of relevance. The patient has

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no prior history of headaches and has a very healthy medical history. He is not taking any medications, has no allergies, has no surgical history, and his family medical history in unremarkable. He mentions that, prior to going on vacation, he had spent a few days working outside, was bitten by a few mosquitoes, and may have had a tick bite but never noted a tick. The patient further explains that it was 2 d prior to presenting to the clinic (and 2 d after the initial symptoms), while flying home from his vacation, when he noted the rapid onset of the fatigue and weakness. Upon arriving at his home destination, he was actually so weak that he needed wheelchair assistance to get to his parked vehicle. The weakness gradually worsened; it started mainly in the lower extremities, but now has spread to involve the hips as well.

2. Given meningeal findings (headache) and worsening, progressive weakness, what would be the most appropriate step after improvement with intravenous fluids and Toradol?

A. Release to home on quarters with duties not to include flying.
B. Hold for observation and additional fluid resuscitation.
C. Order a magnetic resonance imaging of the brain.
D. Admit to the hospital for full diagnostic evaluation.

ANSWER/DISCUSSION

2. D. Admit to the hospital for full diagnostic evaluation. The patient presented with a very concerning clinical picture, including a high fever, rapid progression, and early indications of a possible ascending paralysis. In conjunction with a persistent headache, the patient is at significant risk of neuroinvasive disease that may lead to long-term sequelae, permanent disability, or death in severe cases.

The patient is admitted to the regional hospital for further evaluation. A complete blood count is repeated with a slight elevation in white blood cell count ($11.2 \times 10^3/mm^3$), but is otherwise normal. A basic metabolic panel was essentially normal with the exception of a slight hyponatremia. A computed tomographic (CT) scan was performed to exclude increased intracranial pressure or a mass lesion and was noted to be normal. A lumbar puncture was then performed. Clear fluid with no visible blood was obtained and the opening pressure was normal at 180 mmH_2O. A cerebrospinal fluid (CSF) analysis was completed showing a negative Gram stain and cultures would eventually return normal. CSF protein was mildly elevated and a slight leukocytosis was noted with a lymphocytic predominance. CSF glucose levels were reported as normal. An immunoglobulin M (IgM) antibody-capture enzyme-linked immunosorbent assay was sent off for analysis.

3. Taking into consideration the history and available results, which diagnosis is now most likely in this patient?

A. West Nile (WN) viral meningitis.
B. Meningococcal meningitis.
C. Lyme neuroborreliosis.
D. Coccidioidal meningitis.

ANSWER/DISCUSSION

3. A. West Nile viral meningitis. Given the constellation of clinical presentation and findings, this case suggests a diagnosis of WN viral meningitis.

Meningococcal meningitis is the second most common cause of community-acquired adult bacterial meningitis in the United States (*Streptococcus pneumoniae* is the predominant cause).[27] Blood cultures are positive in 50–60% of cases and CSF cultures have positive growth in 80–90% of all cases.[6] Gram stain of the CSF fluid is the first step and will reveal the organism. Classic bacterial meningitis also includes a low glucose concentration (below 45 $mg \cdot dl^{-1}$), an elevated protein concentration (greater than 500 $mg \cdot dl^{-1}$), and an elevated white blood cell count (> 1000/μl). This patient's laboratory analysis does not support a bacterial etiology for his condition.

Lyme neuroborreliosis is an unlikely complication of Lyme disease caused by the bite of tick-carrying *Borrelia burgdorferi*. The classic triad of neurological Lyme disease includes meningitis, cranial neuritis (particularly facial palsy), and radiculoneuritis (sensory and/or motor findings). CSF analysis most commonly reveals a modest pleocytosis, a moderately elevated CSF protein, and a relatively normal glucose concentration. Although Lyme disease has progressively expanded across the United States to include more than just the eastern coastal regions, the clinical picture and laboratory findings are less suggestive of this diagnosis.

Coccidioidal meningitis is a fungal disease caused by the fungi of the *Coccidioides* genus and is endemic to the desert regions of the southwestern United States and Central and South America. Coccidioidal meningitis is a low-risk complication of infection, but can be very lethal, with an untreated death rate of nearly 95% in 2 yr. Cranial CT scans may reveal hydrocephalus, basilar meningitis, and even cerebral infarction. CSF analysis will often reveal leukocytosis, depressed CSF glucose, and elevation of CSF protein. This diagnosis is very unlikely in this patient given a lack of exposure/travel history and a normal CT scan.

Soon after the CSF analysis was complete, the IgM antibody-capture enzyme-linked immunosorbent assay results returned positive for IgM to the WN virus, confirming the hospital physician's and your suspicions. At the time the patient presented it was also known that a recent outbreak of WN virus infections had begun in the local area. Given the late summer time frame, the patient's admitted exposure to mosquitoes before leaving on vacation, the rapid presentation, and aggressive weakness and fatigue, along with your own community surveillance and awareness, your level of suspicion was high from the beginning. The lab findings only served to confirm what you, as a superb flight surgeon, had surmised.

Primary treatment for WN virus infections is supportive. In cases of WN meningitis, more aggressive treatments have shown some benefit in improving outcome and have included interferon, ribavirin, and intravenous immunoglobulin.

West Nile virus infections were first noted in the United States in 1999 and became a growing concern after the turn of the century, with major outbreaks starting in 2002.[7,11,12,28] It is now considered endemic in North America.[13,32] West Nile virus is a member of the Japanese encephalitis virus group and is spread most commonly by mosquito-to-human transmission. Most cases of infection lead to a

very minimal clinical picture and often go unnoticed or include malaise, myalgia, rash, and a low fever.[1,2,10,21] Recent outbreak surveillance has shown varying rates of the development of the more concerning neuroinvasive disease, with rates between 2.9 and 7.3 per 100,000 cases. Mortality among patients with meningitis and encephalitis is approximately 10%, but has been reported as high as 20% in some outbreaks.[4,20,23–26]

Prognosis following WN infection is extremely variable, with long-term sequelae occurring mainly in those who suffered from the neuroinvasive condition.[5,14,15,22] Persistent symptoms can include somatic complaints (one-third of all patients)[3,8] such as fatigue, memory problems, extremity problems (weakness, numbness or tingling, and pain or myalgia), word-finding difficulty, loss of concentration, lightheadedness, and headaches. A longitudinal cohort study noted that 40% of patients still report symptoms, including fatigue, weakness, and depression, 8 yr after the initial infection.[9,16,17]

Your patient spent the next few days in the hospital being aggressively managed with intravenous immunoglobulin therapy and fluid resuscitation before being discharged to home after a full recovery. Within a week this aviator was back in your flight medicine clinic wanting to know when he can go back to flying. After taking a thorough history since the time of discharge and completing a follow-up examination, it appears that the flyer has made a full recovery, as all findings are normal and the flyer denies any further complications.

4. What advice do you give him?

A. Inform him that when he feels better he can go right back to flying.
B. Gently break the news that his flying days are over.
C. Scratch your head and call the major command for direction.
D. Consult the Air Force Medical Standards Directory and Waiver Guide.

ANSWER/DISCUSSION

4. D. Consult the Waiver Guide. According to the Medical Standards Directory, meningitis and other infectious diseases of the central nervous system are disqualifying and require a waiver.* The U.S. Air Force Waiver Guide makes a distinction between simple aseptic meningitis and other forms of meningoencephalitis. If the clinical course is relatively short and uncomplicated, no abnormal brain function is noted, and laboratory findings are consistent with a mild viral infection, then the diagnosis of aseptic meningitis is appropriate. These cases can be submitted for a waiver with the Aeromedical Consultation Service (ACS) requesting a review/evaluation only for Flying Class I/IA individuals. Any condition more complicated than a simple aseptic meningitis (WN virus being specifically noted in the Waiver Guide) requires a waiver and a full evaluation at the ACS. As of May 2015, 77 cases have been submitted for waivers, with only 6 being denied.[33]

Neither the U.S. Navy nor the Army includes meningitis or WN virus infections as a specific diagnosis in their waiver guides, but do include guidance for possible persistent conditions after resolution of the original infection. Headaches, if meeting the designated criteria outlined in the waiver guides, are considered disqualifying and require a waiver.[18,29] In the case of our flyer, he would be disqualified and would need an evaluation by the branch-specific neurological division prior to consideration for a waiver. Peripheral neuropathies secondary to the WN infection would be considered for a waiver if persistent and would be determined on a case-by-case basis.[19,30]

The pilot in this case was clinically followed for 1 yr before his case was submitted to the ACS for review. At the time of his evaluation, he was found to have a full remission of all symptoms associated with his prior infection. There were no residual neurological deficits, no psychological findings, and no long-term sequelae. The decision was made to recommend that this flyer be granted an indefinite Flying Class II waiver and be returned to his flying duties as soon as possible.

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