Aerospace Medicine Clinic

This paper was prepared by Amy J. Kreykes and Johnene Vardiman, LCDC, SAP.

You are seeing an obese 58-yr-old commercial airline pilot in a fitness for duty case requested by his employer. The last month he has been calling in sick frequently, even canceling remaining legs of his trips due to extreme fatigue. He denies any other symptoms. He falls asleep easily and has no issue staying asleep. He estimates averaging 7 h of sleep each night. He reports compliance with nightly continuous positive airway pressure (CPAP) for his severe obstructive sleep apnea (OSA). He denies any gross hematuria, or bloody or black stools. His past medical history is notable for well controlled hypertension on lisinopril. He denies tobacco, alcohol, or substance use. He has brought his most recent lab work from a routine visit with his primary care physician 2 wk ago, notable for a normal complete blood count (CBC) with differential, normal thyroid stimulating hormone, free T4, and mildly elevated triglycerides.

On examination, he is obese (body mass index 32), pleasant, and conversant. His neurological examination is normal. Fundoscopic examination is normal. There is no organomegaly. He has no changes to his skin, nails, or hair. He has a large neck and a Class III Mallampati Score. Examination is otherwise unremarkable.

1. Based on his history and presentation, what is the best next step?
   A. Obtain the following labs: hemoglobin electrophoresis, iron studies, haptoglobin, lactate dehydrogenase, bilirubin, B12, and folate levels.
   B. Overnight polysomnography testing (PSG).
   C. Assess efficacy of CPAP treatment for obstructive sleep apnea.
   D. Multiple Sleep Latency Testing (MSLT).
   E. Maintenance of Wakefulness Testing.

ANSWER/DISCUSSION

1. C. The patient has a known history of OSA and reports compliance with CPAP treatment. This should be verified by obtaining device log history before considering the other options. The lab studies in answer A assess for causes of anemia. The patient's most recent CBC was normal. Before initiating specific testing for anemia, a CBC with differential should be assessed for the presence of anemia and used to determine if it is microcytic [mean corpuscular volume (MCV) < 80 fL], normocyctic (MCV 80–100 fL), or macrocytic (MCV > 100 fL) to focus follow-up testing.[9] Common causes of anemia include: microcytic—iron deficiency and thalassemia; normocytic—chronic disease/inflammation and pure red cell aplasia; and macrocytic—folate or B_{12} deficiency, myelodysplastic syndromes, and alcohol abuse.[16,17,21] PSG is diagnostic for OSA and used to titrate treatment with CPAP. MSLT, typically performed the day after PSG, measures the tendency to fall asleep through multiple 20-min naps at 2-h intervals.[12] Conversely, Maintenance of Wakefulness Testing measures the patient's ability to stay awake in a dark, quiet room during timed periods at 2-h intervals.[2] This airman has already completed PSG and MSLT since he is being treated with CPAP. It may be necessary to repeat these in the future, but they are not the best next step.

The airman provides a copy of the cumulative annual CPAP report from his device. The actual time he uses the device averages 80% of sleep periods and approximately 7 h per sleep period. Records from his device and a letter from a recent visit with his sleep specialist 2 wk ago indicate that his CPAP settings are adequate.

2. An Aviation Medical Examiner can complete an Aviation Medical Examiner Assisted Special Issuance for OSA provided the airman has initial authorization granted by the Federal Aviation Administration (FAA), signs the Airman Compliance with Treatment Form, provides a current status report from the treating physician, and device data shows actual usage time of:
   A. At least 70% of sleep periods and an average minimum of 5 h of sleep per period.
   B. At least 75% of sleep periods and an average minimum of 6 h of sleep per period.
   C. At least 80% of sleep periods and an average minimum of 7 h of sleep per period.
   D. At least 90% of sleep periods and an average minimum of 7 h of sleep per period.

DOI: https://doi.org/10.3357/amhp.5726.2021

ANSWER/DISCUSSION

2. B. Additionally, for an airman with an established diagnosis of OSA but no recording capability of their CPAP device, a 1-yr exception is granted if the airman provides a personal statement indicating regular use of the CPAP before each shift in which they perform flight or safety duties. For airmen treated with dental and/or positional devices, the airman must be free of comorbid conditions and if the devices have monitoring capability, records must be submitted. For airmen treated with surgery, an attestation statement of persistent absence of OSA symptoms is required.[4]

After receiving the records indicating adequate control of his OSA, you call to follow up with the airman. He reports that he now has a throbbing headache "all over his head," 4/10 intensity. He has not tried anything for it and states he has been doing a lot of yard work outside in the heat the last 2 d without drinking enough water. You advise him to take acetaminophen, stop the yard work, drink more water, and get some rest, but also provide callback precautions. The airman calls you 6 d later. The headache has continued intermittently since your last call, but over the last 2 d it has been constant, generalized/diffuse throbbing pain, with radiation into the neck and photophobia. He also reports intermittent blurry vision, dizziness, and nausea over the last few days. He denies vomiting.

3. Based on the new complaint, what is your recommendation to your airman?
   A. Take acetaminophen 1 g by mouth, get a good night's sleep, and call you in the morning.
   B. Take ibuprofen 800 mg, drink a full glass of water, and lie in a dark, quiet room for an hour.
   C. Report to your clinic for migraine treatment with intravenous fluids, ketorolac, and prochlorperazine.
   D. Go to the Emergency Department.

ANSWER/DISCUSSION

3. D. The airman's symptoms have significantly worsened despite over-the-counter medications. He needs to be seen. The now constant nature of his headache with dizziness, blurred vision, and radiation down the neck are concerning red flags.[2] Although it is possible that these symptoms are an atypical migraine, the differential diagnosis includes life-threatening issues such as cerebrovascular accident, infectious etiology, intracranial mass, and subarachnoid hemorrhage. He should be sent to the Emergency Department for assessment. Atypical migraine must be a diagnosis of exclusion.

You meet the airman and his wife at the Emergency Department. His wife adds to the history that at times he has seemed mildly confused and that he has been intermittently sweating and chilled at home. She denies noticing any facial droop, slurred speech, or changes in his gait. There has been no trauma. His vital signs are normal. Physical exam performed by the Emergency Physician is notable only for photophobia (neurological examination included cranial nerves II–XII, motor, sensory, and coordination components. Fundoscopic examination was not performed. You request that the patient complete a Mini-Mental State Examination. He scores 28/30, losing 2/3 points for recall.

You are concerned that the headache is radiating into his neck, especially given his subjective sweats and chills at home, despite being afebrile now.

4. What physical exam techniques could you add to investigate your hunch?
   A. Assess for Kernig and Brudzinski signs.
   B. Rhomberg sign.
   C. Pinprick sensation.
   D. Rapid alternating movements.

ANSWER/DISCUSSION

4. A. Kernig and Brudzinski meningeal sign examination techniques have been widely criticized due to their documented poor sensitivity (23%, 28%, respectively).[1,10,24] This indicates that when these maneuvers are negative, it does not rule out meningitis. However, the high specificity of Kernig (91%) and Brudzinski's (89%) signs makes them useful for ruling in the possibility of meningitis (i.e., if these tests are positive, there is a high likelihood of meningitis).[10,11] When present, Kernig and Brudzinski signs have a high positive predictive value.[22] Kernig's sign is performed with the patient supine with the hip and knee both flexed to 90°. The knee is then passively extended. Pain and restricted extension past 135° constitutes a positive test.[10] Brudzinksi's sign is performed with the patient supine by passively flexing the neck with one hand, while preventing the torso from rising off the examination table with the opposite hand. Reflexive flexion of the hips and knees constitutes a positive test.[10] Rhomberg sign (balancing for 30 s with eyes closed and feet together) is traditionally performed to assess for pathology in the dorsal column of the spinal cord, but it involves inputs from the vestibular apparatus and cerebellum as well.[18] Pinprick sensation is performed to assess for spinothalamic tract lesions in the spinal cord.[5] Rapid alternating movements assess for cerebellar lesions.[15]

Your airman had positive Kernig and Brudzinski signs on repeat examination. His serum laboratory values (CBC with differential, complete metabolic panel, thyroid stimulating hormone, lipid panel) were normal except for mildly elevated triglycerides. A computed tomography scan of his head without contrast was unremarkable. Neurology was consulted. Magnetic resonance imaging/magnetic resonance angiography of the brain was unremarkable. A lumbar puncture was obtained and cerebrospinal fluid (CSF) analysis was consistent with aseptic meningitis.

5. Which of the following patterns of CSF analysis is consistent with aseptic meningitis?

Table I. CSF Analysis Patterns by Disease State.[13,14]

DISEASE STATE	COLOR	OPENING PRESSURE (mm H_2O)	WBC/mm^3*	PREDOMINANT TYPE OF WBC	GLUCOSE (mg/dL)	PROTEIN (mg/dL)
Normal	Clear	60–250	0–5	Lymphocytes	50–75[§]	18–58
Bacterial	Cloudy	Elevated	>1000 (87%)[†] >100 (99%)[†]	Polymorphonuclear cells	<45	21–2220 (Avg. 418)
Aseptic	Clear	Normal	<300	Lymphocytes[‡]	50–100	11–400 (Avg. 77)
Fungal	Cloudy	Variable	<300	Lymphocytes	<45	40–300
Tuberculosis	Cloudy	Variable	<500	Lymphocytes	<45	100–200

CSF: cerebral spinal fluid; WBC: white blood cells.
*Note that traumatic spinal taps increase WBCs in the CSF on average 1 WBC for every 500-1000 RBCs, assuming a normal peripheral WBC count (American Academy of Family Physicians).
†87% of patients with bacterial meningitis have a more than 1000 WBCs in the CSF and 99% have more than 100 WBCs.
‡In drug-induced cases of aseptic meningitis, there is typically a predominance of polymorphonuclear cells.
§The glucose level in normal CSF is approximately 2/3 of the glucose level in peripheral blood (American Academy of Family Physicians).

A. Cloudy, variable opening pressure, 400 WBC/mm^3, predominantly lymphocytes, 40 mg/dL glucose, and 150 mg/dL protein.
B. Clear, normal opening pressure, 2 WBC/mm^3, predominantly lymphocytes, 63 mg/dL glucose, and 45 mg/dL protein.
C. Cloudy, normal opening pressure, 150 WBC/mm^3, predominantly lymphocytes, 30 mg/dL glucose, and 90 mg/dL protein.
D. Cloudy, elevated opening pressure, 1500 WBC/mm^3, predominantly polymorphonuclear cells, 20 mg/dL glucose, and 400 mg/dL protein.
E. Clear, normal opening pressure, 115 WBC/mm^3, predominantly lymphocytes, 60 mg/dL glucose, and 159 mg/dL protein.

ANSWER/DISCUSSION

5. E. These values are the airman's. The classic CSF pattern for aseptic meningitis is clear fluid, a normal opening pressure, fewer than 300 WBC/mm^3 with a predominance of lymphocytes, glucose between 50–100 mg/dL, and an average protein of 77 mg/dL.[13,14] (see **Table I**). Answer A corresponds to tuberculosis meningitis. Answer B is normal CSF. Answer C is fungal meningitis. Answer D is bacterial meningitis.

Aseptic meningitis encompasses nonbacterial and nonfungal etiologies. The most common causes of aseptic meningitis are viral, with enteroviruses and herpes simplex virus type 2 being responsible for most cases in adults.[8,22] Noninfectious causes include drug-induced reactions (most commonly trimethoprim-sulfamethoxazole, but also other antimicrobials—amoxicillin and cephalosporins—valacyclovir, and immunosuppressive medications), malignancy, vasculitis, and auto-immune disorders such as rheumatoid arthritis and systemic lupus erythematous.[7,22,23] In cases of drug-induced aseptic meningitis, the CSF white blood cells can have either a lymphocytic or polymorphonuclear predominance.[23] Symptoms in adults, as seen in our airman, typically include a throbbing headache, photophobia, and fever. Nausea, vomiting, and neck stiffness are also commonly reported.[22]

Viral aseptic meningitis shows a seasonal spike in summer and fall in temperate climates, but is present year-round in tropical climates.[22] Transmission is primarily via the fecal-oral route.[22] Polymerase chain reaction is the gold standard for viral meningitis diagnosis. Symptoms typically resolve rapidly over a period of 1–2 wk.[22,23] Treatment for aseptic meningitis is primarily supportive, but some viral cases benefit from antiviral treatment.[22]

Your airman remained afebrile without antipyretics during his week-long hospital stay. Initially he was treated with antibacterial and antiviral broad-spectrum coverage for meningitis. Antibiotics were stopped after the CSF analysis and gram stain returned negative for bacteria. The CSF culture never grew bacteria. Antiviral treatment was discontinued after 48 h when no causative viral agent could be identified. Drug-induced aseptic meningitis was considered unlikely. The airman received supportive treatment and recovered fully within 2 wk. Initial electroencephalogram (EEG) was notable for mild generalized slowing, a nonspecific finding that can occur with aseptic meningitis. He never had seizures. Repeat EEG before discharge was normal.

The FAA, Army, and Air Force will consider resolved aseptic meningitis cases for special issuance and retention waivers on a case-by-case basis.[3,6,19] The Navy makes no mention of meningitis in their waiver guide.[20] Notably, the Air Force only considers "aseptic meningitis" to include cases without alteration in cognitive function. They would consider this airman to have had a more severe diagnosis of meningoencephalitis.[6]

The airman was grounded. He underwent a complete rheumatological work-up to rule out vasculitis and auto-immune/auto-inflammatory disorder. Neurocognitive testing was performed and was normal. He was re-evaluated by a neurologist and a repeat lumbar puncture revealed a normal CSF analysis and repeat EEG remained normal. He was also re-evaluated by his sleep specialist and a psychiatrist. He is resubmitting to the FAA for special issuance.

Kreykes AJ, Vardiman J. ***Aerospace medicine clinic: aseptic meningitis.*** **Aerosp Med Hum Perform. 2021; 92(10):845–848.**

REFERENCES

1. Akaishi T, Kobayashi J, Abe M, Ishizawa K, Nakashima I, et al. Sensitivity and specificity of meningeal signs in patients with meningitis. J Gen Fam Med. 2019; 20(5):193–198.
2. Cutrer MF, Wippold II FJ, Edlow J. Evaluation of the adult with nontraumatic headache in the emergency department. UpToDate. 2019. [Accessed June 2021]. Available from https://www.uptodate.com/contents/evaluation-of-the-adult-with-nontraumatic-headache-in-the-emergency-department.
3. Federal Aviation Administration. Guide for Aviation Medical Examiners: item 46. Neurologic - infections of the nervous system. [Accessed 28 June 2020]. Available from https://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/app_process/exam_tech/item46/amd/infections/.
4. Federal Aviation Administration. Guide for Aviation Medical Examiners: special issuances AME assisted - all classes - obstructive sleep apnea (OSA). [Accessed 27 June 2020]. Available from https://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/special_iss/all_classes/sleep_apnea/.
5. Haefeli J, Kramer JLK, Blum J, Curt A. Assessment of spinothalamic tract function beyond pinprick in spinal cord lesions: a contact heat evoked potential study. Neurorehabil Neural Repair. 2014; 28(5): 494–503.
6. Hesselbrock R, Van Syoc D, Gregory D. Air Force waiver guide: meningitis and encephalitis. Washington (DC): U.S. Air Force; May 13, 2020.
7. Holle D, Obermann M. Headache in drug-induced aseptic meningitis. Curr Pain Headache Rep. 2015; 19(7):29.
8. Kupila L, Vuorinen T, Vainionpää R, Hukkanen V, Marttila RJ, Kotilainen P. Etiology of aseptic meningitis and encephalitis in an adult population. Neurology. 2006; 66(1):75–80.
9. Maner BS, Moosavi L.Mean corpuscular volume (MCV). Treasure Island (FL): StatPearls Publishing; 2020. [Accessed 28 June 2020]. Available from http://www.ncbi.nlm.nih.gov/books/NBK545275/.
10. Mehndiratta M, Nayak R, Garg H, Kumar M, Pandey S. Appraisal of Kernig's and Brudzinski's sign in meningitis. Ann Indian Acad Neurol. 2012; 15(4):287–288.
11. Nigrovic LE. Aseptic meningitis. In: Dulac O, Lassonde M, Sarnat HB, editors. Handbook of clinical neurology, pediatric neurology, part II, vol. 112, chapter 119. Amsterdam (Netherlands): Elsevier; 2013:1153–1156.
12. Pickard JS, Gray GW. Respiratory diseases: aeromedical implications. In: Fundamentals of aerospace medicine, 4th ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2011:306–317.
13. Sabatine MS. Pocket Medicine, 4th ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2011.
14. Seehusen DA, Reeves M, Fomin D. Cerebrospinal fluid analysis. Am Fam Physician. 2003; 68(6):1103–1108.
15. Stanford. Cerebellar exam. Stanford Medicine 25. [Accessed 27 June 2020]. Available from https://stanfordmedicine25.stanford.edu/the25/cerebellar.html.
16. Tefferi A. Anemia in adults: a contemporary approach to diagnosis. Mayo Clin Proc. 2003; 78(10):1274–1280.
17. Tefferi A. Practical algorithms in anemia diagnosis. Mayo Clinic Proc. 2004; 79(7):955–956.
18. Turner MR. Romberg's test no longer stands up. Pract Neurol. 2016; 16(4):316.
19. U.S. Army. Army Regulation 40-501. Medical Services Standards for Medical Fitness. Washington (DC): U.S. Army; June 27, 2019.
20. U.S. Navy. U.S. Navy Aeromedical Reference and Waiver Guide. Washington (DC): U.S. Navy; April 27, 2020.
21. Weiss G. Anemia of chronic disease. N Engl J Med. 2005; 352(10):1011–1023.
22. Wright WF, Pinto CN, Palisoc K, Baghli S. Viral (aseptic) meningitis: a review. J Neurol Sci. 2019; 398:176–183.
23. Yelehe-Okouma M, Czmil-Garon J, Pape E, Petitpain N, Gillet P. Drug-induced aseptic meningitis: a mini-review. Fundam Clin Pharmacol. 2018; 32(3):252–260.
24. Zuger A. Kernig and Brudzinski fail to perform. NEJM Journal Watch. 2002. [Accessed 27 June 2020]. Available from https://www.jwatch.org/JW200207050000002/2002/07/05/kernig-and-brudzinski-fail-perform.