You're the Flight Surgeon

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You're a Navy flight surgeon on deployment in Okinawa with a P-8A squadron (a maritime patrol plane similar to a 737). Your phone rings and on the other end of the line is a distraught pilot. His vision is blurry, he is feeling numbness and tingling in his legs, and he is having trouble walking. He does not think he can make it to the clinic, which is a short flight of stairs away. You arrive at his room and find him holding onto the walls for support. He tells you that over the last 24 h he has been unwell and woke up this morning with feelings of gait unsteadiness and double vision.

A brief history reveals that this is a 27-yr-old Caucasian man with no significant past medical or surgical history. He is not taking any medication or supplements. He has been recently stationed in Okinawa and he has an extensive travel history to different detachment sites around Southeast Asia that include the Philippines and Thailand in the last 3 mo. He has no known sick contacts. He denies slurred speech or difficulty swallowing; nausea, vomiting, or diarrhea; chest pain or shortness of breath; headache or neck pain; or any rashes or skin findings. He also denies fever or chills, but endorses a sore throat, which has been bothering him for the last 2 wk. He has had no recent immunizations.

The patient is transported to the clinic where his physical exam reveals the following: temperature 99.2°F, blood pressure 115/78, heart rate 82, respiratory rate 16, and pulse oximetry of 96% on room air. He appears tired and worried, but healthy. His eye exam reveals abnormal extraocular movements with bilateral external ophthalmoplegia. He reports horizontal diplopia worsening with lateral gaze. His pupils are mildly atonic with a sluggish reaction to light bilaterally. He has normal tympanic membranes that demonstrate normal mobility, patent nares without erythema or discharge, and a supple neck without cervical lymphadenopathy. His lungs are clear to auscultation without wheezes or rhonchi, and his heart demonstrates a regular rate and rhythm with no rubs, murmurs, or gallops. His abdomen is soft, nontender, and nondistended with no organomegaly. His extremities have normal strength and movement on exam; however, you are unable to elicit deep tendon reflexes and his gait is ataxic. He exhibits no peripheral edema and has strong peripheral pulses. His skin exam reveals no lesions.

1. How does one differentiate between monocular and binocular diplopia?

A. Determine if the image is separated horizontally, vertically, or both.
B. Cover each eye, individually, during the examination.
C. Determine if the diplopia changes with near vision testing.
D. Perform a slit lamp examination.

ANSWER/DISCUSSION

1. B. To determine the difference between monocular and binocular diplopia, simply cover each eye and determine if the abnormal vision persists. Monocular diplopia generally represents a problem with refraction in the affected eye, whereas binocular diplopia generally represents a neurological deficit. During the examination, determine if the images are separated vertically, horizontally, or both, and carefully note the different movements of the globe. The extraocular muscles are innervated by the third, fourth, and sixth cranial nerves, and any lesion associated with these nerves will produce characteristic findings.

2. What are the characteristic findings for an isolated third cranial nerve palsy?

A. "Down and out": the affected eye has a blown pupil and is deviated to the inferior lateral position.
B. Patient will come to the clinic with a tilted head, which tilts away from the lesion. This is because of the "cyclotorsion" effect of the muscle on the orbit.
C. Patient is cross-eyed and turns his or her head while tracking objects to avoid diplopia caused by lateral gaze.
D. Pain with eye movement, decreased color and contrast sensitivity, and an afferent pupil defect.

ANSWER/DISCUSSION

2. A. The characteristic finding for an isolated third cranial nerve lesion is the "down and out" appearance of the affected eye. Notably, the third cranial nerve also innervates the levator palpebrae, which causes significant ptosis in the affected eye. Answer B describes an isolated fourth cranial nerve lesion and answer C describes an isolated sixth cranial nerve lesion.

Cranial nerve lesions are not the only pathological entities that can produce these findings. The differential is broad and includes

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mitochondrial myopathies, oculopharyngeal dystrophy, myotonic dystrophy, thyroid eye disease, and cases of myasthenia gravis.[1] It is important to note that lesions affecting the third cranial nerve will typically present with pupillary involvement because the parasympathetic nerves controlling pupil constriction travel with the third nerve. Pupillary involvement will not accompany mitochondrial myopathies, oculopharyngeal dystrophy, myotonic dystrophy, thyroid eye disease, and cases of myasthenia gravis. Any associated pain should be noted. It is important to differentiate between pain with and without movement of the globe.

During your examination, this patient has relative ophthalmoplegia with binocular diplopia. The patient describes a horizontal separation of the images with lateral gaze and both eyes appear to be equally affected.

3. Given the patient's current symptoms, what is the most appropriate next step?

A. Observation.
B. Outpatient Neurology consult.
C. Outpatient Ophthalmology consult.
D. Head computed tomography at the nearest emergency room.
E. Lumbar puncture.

ANSWER/DISCUSSION

3. D. In the acute setting, it is important to rule out a mass lesion or stroke, which could be causing this patient's deficits. In our case, the patient's computed tomography scan revealed no masses or acquired vascular lesions. Further work-up in the hospital included a Neurology consultation at the bedside, as well as a brain magnetic resonance imaging and a lumbar puncture. Neurological examination confirmed the bilateral external ophthalmoplegia, ataxia, and areflexia. The MRI was unremarkable and the cerebrospinal fluid showed elevated protein. Fatigue-ability with up-gaze testing was negative.

4. What is the most likely diagnosis at this time?

A. Multiple sclerosis.
B. Miller Fisher syndrome.
C. Myasthenia gravis.
D. Vascular aneurysm.
E. Wernicke encephalopathy.

ANSWER/DISCUSSION

4. B. Miller Fisher syndrome (MFS) is characterized by a triad of neurological signs: extraocular muscle paralysis, limb ataxia, and tendon reflex loss. This clinical entity was first described in 1956.[5] MFS is considered a variant of Guillain-Barré syndrome (GBS) and accounts for 5–10% of GBS cases, with an annual incidence of 0.09/100,000 population[6] compared to 1-2/100,000 for GBS. Interestingly, the reported incidence of MFS appears to have a geographic variation, with a higher proportion of MFS among GBS patients in the Far East,[8] particularly in Japan,[11] where MFS made up 25% of GBS patients, and in Tawain,[16] where MFS made up 18% of reported GBS. MFS is more common in men and affects people of all ages, with the median age of onset being in the fifth decade.[7]

MFS is typically a self-limited syndrome and in most cases all symptoms resolve spontaneously. The clinical onset, nadir, and spontaneous recovery that occur are highly suggestive of an acute phase primary immune response.[9] It is generally believed that MFS follows an infectious process and several such processes, including *Campylobacter jejuni* and viral upper respiratory infections, have been linked to MFS. The clinical symptoms peak at 10 to 14 d after an infectious event.[15]

5. MFS is strongly associated with the presence of which of the following proteins?

A. Antidouble stranded DNA.
B. Rheumatoid factor.
C. Aquaporin 4.
D. Anti-GQ1b antibody.
E. Antithyroglobulin antibody.

ANSWER/DISCUSSION

5. D. Anti-GQ1b antibody is associated with 90% of MFS patients and was positive in this patient as well. Although data strongly support the principle of molecular mimicry between GQ1b/GT1a and *C. jejuni* lipopolysaccharide, the link between viral pathogens and GQ1b is less clear. Viruses do not encode glycosylating enzymes. It is suggested that viral proteins may become glycosylated with ganglioside-mimicking oligosaccharides in the respiratory epithelium.[15] The molecular mimicry sets the stage for an autoimmune response, resulting in the symptoms of MFS.

Treatment of MFS is unclear. A literature search revealed no evidence of prospective studies pertaining to the treatment of MFS. Anecdotal evidence suggests use of plasmapheresis and intravenous immunoglobulin (IVIG), but reported use has had mixed results. A series of 50 consecutive cases showed no benefit of using plasmapheresis versus a placebo.[10] Two case studies have demonstrated some treatment benefit with the use of IVIG; however, both of these case reports also suggest that this treatment should be reserved for cases where the patient develops respiratory difficulties or cranial nerve 9-12 involvement (difficulty swallowing, speaking).[2,17]

From an aeromedical standpoint, after resolution of the symptoms, the patient may be considered for a waiver, and the waiver process follows that for GBS for all three services.[3,12,14] To be considered for a waiver, the patient must no longer have any residual ocular symptoms and, although areflexia may persist, the patient must have full strength and function in all motor groups as well as an assessment of his autonomic nervous system function.

There are two case reports of MFS in the aeromedical literature: a third class airman and a pilot. The third class airman was granted an Authorization for Special Issuance of a third class medical certificate due to the history of GBS. His case was particular, however: his symptoms did not completely resolve, leaving him with a persistent esophoria (corrected with the use of authorized lenses).[13] The other patient, a pilot, had complete resolution of his symptoms and was returned "to full flight duties" after an observation period of 2 yr.[4]

Our patient was hospitalized for 7 d and discharged from the hospital in Okinawa after a 5-d course of IVIG. On discharge the patient had a normal ophthalmologic exam and his ataxia had completely resolved. His only remaining neurological deficit was persistent areflexia. He was sent home to his home base in Jacksonville, FL. This patient's areflexia completely resolved 1 mo after the onset of his symptoms and, after passing autonomic testing and a treadmill exercise test, he was recommended for a waiver to return to full flight status as a pilot. His waiver was granted 2 mo after the onset of his symptoms.

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A 29-yr-old female flight test engineer reports to the flight medicine clinic with a history of fatigue, headache, nausea, and skin sensitivity. Her symptoms were present for many weeks but have recently worsened. Patient denies fevers, chills, recent travels, contact with ill persons, or history of trauma. Past medical history is significant for history of pancreatitis as a child. Past surgical history included wisdom tooth extraction. She takes over-the-counter multivitamins, but no prescription medications. The patient is not pregnant.

1. What is an appropriate next step in the work-up?

A. Detailed history and physical.
B. Complete metabolic and hematologic work-up including a thyroid panel.
C. Computed tomography and magnetic resonance imaging studies of the brain.
D. Behavioral health referral.

ANSWER/DISCUSSION

1. A. Detailed history and physical. The patient appears to have symptoms associated with multiple diseases without a unifying diagnosis. She has been a flight test engineer for 4 yr and denies significant changes in her crew duties. The aviator states that she has been training for an ultra-marathon and has lost approximately 5 lb over the course of 2 wk. She also reports a past medical history of chronic subclinical

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