You're the Flight Surgeon

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A 26-yr-old Chinese male C-130 flight engineer with no past medical history of note presented with gradual onset weakness and numbness of his right palm, which progressed to involve his right lower limb over 2 wk, eventually affecting his ability to ambulate and climb stairs. He sought medical attention at the local emergency department and was hospitalized on the same day. Physical examination revealed a right pronator drift, dysmetria, and hyperreflexia, and muscle power of the right arm was 4+/5 by Medical Research Council grading.

1. Based on this clinical presentation, all of the following are possible differential diagnoses except:

A. Subacute stroke.
B. Central nervous system (CNS) lymphoma.
C. Acute inflammatory demyelinating polyneuropathy.
D. Multiple sclerosis (MS).

ANSWER/DISCUSSION

1. C. Of the four choices, only acute inflammatory demyelinating polyneuropathy presents with a lower motor neuron pattern of weakness, comprising progressive and fairly symmetric muscle weakness accompanied by absent or depressed deep tendon reflexes. The clinical features of this patient were more typical of an upper motor neuron pattern of weakness. Primary CNS lymphoma presenting with periventricular lesions in the brain may occur even in immunocompetent individuals and present with focal neurological deficits.[1] MS can present in a multitude of ways, including long tract symptoms and signs (numbness, weakness, and incoordination). Stroke may also present in a subacute manner, although atypical, as it was not sudden or maximal at onset.

2. All of the following are appropriate initial investigations except:

A. Magnetic resonance imaging (MRI) of the brain.
B. Nerve conduction study.
C. MRI of the cervical spine.
D. Lumbar puncture and cerebrospinal fluid (CSF) investigations.

ANSWER/DISCUSSION

2. B. MRI of the brain, which is highly sensitive and has good spatial resolution, can be used to diagnose most intracranial lesions. Lumbar puncture and CSF analysis would aid in the diagnosis of intracranial infectious diseases (e.g., encephalitis, meningitis), small intracranial hemorrhage, inflammatory or autoimmune diseases, and CNS malignancies. The patient's right-sided incoordination, weakness, and numbness could also be due to cervical spine pathology; hence, an MRI of the cervical spine would be useful. Nerve conduction study would be indicated for suspected peripheral neuropathy, which is the least likely diagnosis in this case.

A noncontrast computed tomography brain scan showed an ill-defined hypodensity in the left corona radiata and left parietal region. Stroke work-up comprising ultrasound carotids and transthoracic echocardiography was negative. Investigations for prothrombotic states, including protein C and S deficiency, factor V Leiden mutation, lupus anticoagulant, and antithrombin III, were negative. The Venereal Disease Research Laboratory screen for syphilis was negative in both serum and CSF. MRI brain scan showed several peripherally enhancing, mildly restricted, and perivenular focal lesions in the subcortical and periventricular white matter, typical for active demyelinating plaques. CSF analysis (cell count 3 units/mm^3, protein 0.19 g $\cdot$ L^{-1} or 19 mg $\cdot$ dL^{-1}, glucose 3.4 mmol $\cdot$ L^{-1} or 61.3 mg $\cdot$ dL^{-1}) was unremarkable and negative for infection. Investigations for viruses, tuberculosis, toxoplasma, and *Cryptococcus* were negative.

The flight engineer was reviewed 2 wk postdischarge in the Aviation Medicine clinic and grounded provisionally pending further investigations. His right-sided neurological symptoms improved initially, but subsequently he developed a new episode of left facial numbness involving the tongue in the distribution of the mandibular branch of the trigeminal nerve (CN V3) 3 wk later. Repeat MRI brain scan showed multiple new ovoid lesions in the corpus callosum, left thalamus, left tectal plate, left middle cerebellar peduncle, bilateral anterior temporal lobes, and left posterior lobe; the old lesions seen previously showed interval improvement. He was diagnosed with MS.

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3. In this case, the following support a diagnosis of MS except:

A. A diagnosis of MS cannot be made if the flight engineer only has one episode of neurological symptoms.
B. CNS lesions disseminated in time and space.
C. While not common, MS can also occur in individuals of Asian descent.
D. Exclusion of stroke.

ANSWER/DISCUSSION

3. A. MS is a chronic immune-mediated inflammatory disease that attacks myelinated axons in the CNS, with lesions disseminated over time and anatomical space.[7] Diagnosis of MS is currently based on the McDonald MS Diagnostic Criteria, which were recently revised in 2017.[15] The diagnostic criteria emphasized demonstration of disseminated lesions in time and space, while excluding alternate diagnoses such as stroke. Using these criteria, the diagnosis of MS can be made based purely on clinical grounds. However, MRI can often support, supplement, or even replace some of the clinical criteria.

MS is an uncommon condition in Asians. The prevalence rate throughout countries in Asia is 12.48 per 100,000 individuals based on a systematic review of 68 MS epidemiological studies in Asia.[4] This ranges from 0.77 per 100,000 individuals in Hong Kong[11] to 85.80 per 100,000 individuals in Iran.[5] It has been observed that MS prevalence is higher in West Asia compared to East and South Asia.[4] No population studies on MS are available in Singapore.

Within a month, the flight engineer acutely developed double vision and hearing loss and was once again admitted to the hospital for another relapse of MS. He was treated with a course of intravenous methylprednisolone for 5 d followed by oral prednisolone taper over 9 d, with complete resolution of symptoms. He was started on interferon β-1a to prevent further relapses. Subsequently, the flight engineer was discharged and has remained relapse-free for more than 2 yr. A repeat MRI showed largely stable demyelinating lesions, with no new plaques and no abnormal enhancement with intravenous contrast.

4. The flight engineer visits you at your Aviation Medicine clinic requesting a return to flying duties. He produces a memo from his attending neurologist stating that he has achieved NEDA, "nil evidence of disease activity." What would you do next?

A. Explain to the flight engineer that the diagnosis of MS is a bar to flying and permanently ground him.
B. Enroll the flight engineer in a military rehabilitation program to regain muscle strength and coordination and return him to flying status once he achieves full functional recovery.
C. Continue to ground the flight engineer temporarily as he continues to follow up with the neurologist and undergo long-term treatment.
D. Return the flight engineer to flying status as he has been cleared by a neurologist to fly.

ANSWER/DISCUSSION

4. C. Due to the introduction of disease modifying therapies (DMTs) for MS, the frequency of relapse and the accumulation of permanent disability have been significantly reduced; hence, the diagnosis of MS may not necessarily be a permanent bar to flying. The treatment of MS, while effective, requires a period of grounding due to side effects with potential aeromedical implications. Treatment options for MS can be divided into treatments for acute attacks and treatments to prevent relapses. For acute attacks, a short course of intravenous methylprednisolone followed by oral prednisolone taper may be used. To prevent relapses, there are different long-term treatment options for relapsing-remitting MS, comprising injectable, oral, and infused medications:

- injectable medications—interferon β-1a, interferon β-1b, daclizumab, glatiramer acetate;
- oral medications—teriflunomide, fingolimod, dimethyl fumarate; and
- infused medications—natalizumab, alemtuzumab, mitoxantrone, and ocrelizumab.[10]

The decision on which DMT to start depends on factors including the side effect profile, preference of orals over injectables, age, gender, and desire for pregnancy.[17] Of note, the side effect profile and the relative efficacy, which will determine the propensity for breakthrough disease, are important aeromedical considerations in the management of an aircrew with MS.

Side effects of MS treatments include localized irritation following subcutaneous injections and intramuscular injections with interferon β and glatiramer acetate. Interferon β therapy has a 50–75% risk of flu-like symptoms[3] and a significant risk of depression,[17] while glatiramer acetate leads to short-duration chest palpitations, chest tightness, flushing, and anxiety. Side effects, if they occur, tend to be largely self-limited and resolve over time. From the aeromedical fitness perspective, all aircrew on MS treatment will need to be assessed not only for disease control, but also full resolution of any iatrogenic side effects before being considered for return to duties.

NEDA is a term introduced in recent years and could well assist clinicians and aeromedical waiver authorities in predicting future disability progression. NEDA comprises three factors: no clinical relapse, no disability progression measured by the Expanded Disability Status Scale for 12 wk, and no evidence of disease activity on MRI.[8] In a 7-yr study, a total of 99 of 215 patients (46%) achieved NEDA at year 1, but only 7.9% maintained NEDA status through year 7. Maintaining NEDA at 2 yr has a positive predictive value of 78.3% for no progression at 7 yr.[14] The prognostic data will be useful to aeromedical waiver authorities in determining the period of grounding for observation of aircrew with MS. While we are mindful not to rely on a few studies alone for aeromedical standards formulation, this provides informative input, especially with the advent of new and more effective treatment modalities.

The flight engineer had 320 h on the C-130. Although not directly in control of the aircraft, he is responsible for the safe operation of flight by monitoring the aircraft's engines and other critical flight systems and adjusting the settings of major flight systems such as fuel, pressurization, air conditioning, hydraulic, electrics, and the engines in flight.

5. The following are aeromedical considerations for a flight engineer with MS except:

A. Neurological deficits impede safe and effective occupational performance.

B. Individuals with MS are at risk of developing seizures.
C. The relapsing nature of MS will have an impact on the ability to safely deploy the flight engineer for operations.
D. Any aircrew with MS should be grounded permanently, as treatment of MS with DMTs is incompatible with flying.

ANSWER/DISCUSSION

5. D. MS is historically considered incompatible with a career in military aviation for multiple reasons, including: 1) cognitive impairments; 2) physical impairments; 3) psychological impairments; and 4) fatigue. MS also has an unpredictable nature and potentially rapid onset of neurological symptoms, which are also considered incompatible with a safe flying environment.[2] Cognitive impairments include difficulty with explicit learning and retrieval of verbal or visuospatial material, difficulties in tasks using working memory, and difficulty in performing tasks demanding attention and rapid information processing.[9] The flight engineer's role in monitoring the major flight systems both in routine flight as well as handling emergencies warrants good cognitive skills. In terms of physical impairments, visual disturbances, bladder dysfunction, ataxia, vertigo, weakness, spasticity, and paresthesia can present over a period as short as a few hours. This will affect the ability of the flight engineer to safely navigate the narrow steps and ladders of the aircraft and execute emergency drills. Bladder dysfunction can be particularly distressing to aircrew, as toilets may not be available. Psychological impairments including depression are reported in about 50% of patients and may worsen with stress.[9] Military aviators work in stressful environments performing military operations or handling aircraft emergencies. Finally, fatigue in MS can be caused by drugs (interferon β), body temperature, depression, and sleep disorders.[18]

Aeromedical disposition of aircrew with MS differs around the world. In the U.S. military, MS is considered disqualifying for military flying, except for certain aviators (Flying Classes II and III) who have recovered from a single, monophasic episode of neurological dysfunction.[12,13,16] For U.S. civil aviation, the Federal Aviation Administration considers a history of or the presence of any potentially incapacitating neurological condition or disease to be initially disqualifying pending further evaluation. For MS, issuance of a medical certificate requires a Federal Aviation Administration decision.[6] In the Canadian forces, the mild relapsing-remitting type of MS does not preclude a pilot from active service, although limitations are applied in terms of deployability and operational flying.[2] The Israeli Air Force also applies an individualized approach to the management of aircrew with MS and returned two pilots with confirmed MS and a navigator with probable MS back to flying duties, as they were assessed to have relatively slow onset of relapses and short flight durations and could be relied upon to report suspicious symptoms. A recommendation to ensure good compliance and reliable means of detection of disease progression was also made.[18]

The treatment and prognostication for MS has improved significantly, with positive results from new clinical trials. With more clinical experience and supporting studies, the paradigm of permanent grounding for aircrew with MS may no longer be the case, given that newer and more effective DMTs, and the ability to prognosticate disease progression based on NEDA, may allow aircrew with well-controlled MS (achieving NEDA at 2 yr) to return to flying.[14]

In summary, MS is an autoimmune demyelinating disease of the CNS that commonly leads to disability in aircrew affected by it. The diagnosis of MS should be considered in persons who present with a subacute onset of an upper motor neuron pattern of weakness. Further evaluation to confirm MS and to rule out other differential diagnoses needs to be carried out in a specialist hospital, with close partnership between the flight surgeon and the neurologist.

While MS is a chronic relapsing disorder and its treatment does have significant side effects of aeromedical concern, more recent concepts in the treatment and prognostication of MS may allow aircrew to return to flying. The determination of an aircrew member's fitness to fly with MS should take into account this new evidence to achieve a more structured approach to assessing aeromedical risk and fitness to fly.

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Erratum

Lerner DJ, Chima RS, Patel K, Parmet AJ. *Ultrasound Guided Lumbar Puncture and Remote Guidance for Potential In-Flight Evaluation of VIIP/SANS*. Aerosp Med Hum Perform. 2019; 90(1):58–62. DOI: https://doi.org/10.3357/AMHP.5170.2019

There is an error in the terminology used in the above article. The term "seated lordotic" is used three times in the article, once in the Abstract Results Section; once in the last sentence of the first paragraph of the Methods section; and in the first sentence of the Results section in the body of the report. The correct terminology should be the "seated exaggerated kyphotic" position.

The authors sincerely apologize for this error and any inconvenience it may cause.