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MORNING REPORT

A 66-Year-Old Man with Fever and Confusion

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Abstract

Morning Report is a time-honored tradition where physicians-in-training present cases to their colleagues and clinical experts to collaboratively examine an interesting patient presentation. The Morning Report section seeks to carry on this tradition by presenting a patient's chief concern and story, inviting the reader to develop a differential diagnosis and discover the diagnosis alongside the authors of the case.

This report examines the story of a 66-year-old man with Parkinson's disease and hypertension who presented to the emergency department with fever and confusion. He had recently travelled from the United States to visit family in Cambodia. On the return flight, his speech became incoherent, and he had rhythmic shaking movements of the arms and legs without gaze deviation, incontinence, or loss of consciousness. Using questions, physical examination, and testing, an illness script for the presentation emerges. As the clinical course progresses, the differential is refined until a final diagnosis is made.

Chana A. Sacks, M.D., M.P.H., Editor

Reason for presentation: confusion

Part 1: The Case

History of Present Illness: A 66-year-old man with Parkinson's disease and hypertension presented to the emergency department with fever and confusion after returning to the United States from Cambodia. In June (6 weeks before this presentation), he had traveled to Cambodia's capital city, Phnom Penh. Three weeks after that, he visited a rural town in the countryside. Ten days before presentation, the patient ran out of all his medications and subsequently developed fatigue and anorexia. Seven days before presentation, his movements slowed.

On the day of presentation, the patient returned to Boston from Cambodia by plane; en route, episodes of confusion, nonsensical mumbling, and rhythmic shaking movements of the arms and legs developed. There was no associated gaze deviation, incontinence, or loss of consciousness. Upon arrival in Boston, the patient was brought directly to the emergency department. At the time of the initial assessment, he was febrile with diaphoresis

and rigors. Additional information about this patient's history, medications, and allergies is shown in Box 1.

Box 1: Medical and Surgical History, Medications, Allergies, and Social History

Medical and Surgical History:

Parkinson's disease, rapid eye movement sleep disorder, hypertension, and hyperlipidemia

Medications:

Neurologic: amantadine, carbidopa-levodopa, and clonazepam

Cardiovascular: atenolol, losartan, aspirin, and atorvastatin

Allergies:

Angiotensin-converting enzyme inhibitors (reaction: cough)

Social History:

The patient was born in Cambodia and had moved to the United States 30 years earlier. He lives with his wife, son, and granddaughter in New England. He has no pets or other wildlife exposures. He works in the biotechnology industry. He does not smoke, consume alcohol, or use other drugs.

WHAT ADDITIONAL QUESTIONS WOULD HELP GENERATE AN INITIAL DIFFERENTIAL DIAGNOSIS?

Q1: In what activities did the patient engage while traveling?

Rationale for question: The evaluation of fever in a returning traveler requires an assessment of all destinations of travel, travel timeline, and environmental exposures to determine potential risks for travel-associated infections.[1] Travelers such as this patient who return to their countries of origin to visit friends and relatives (sometimes referred to as VFR travelers) have disproportionately increased infectious disease risks, which are attributed to a number of factors including a lack of awareness of risk, prolonged stays, and consumption of local food and beverage, among other factors.[2] A comprehensive exposure history includes assessment of water sources for drinking and bathing, food sources and preparation, contacts with animals and insects, recreational activities, and sexual activity and use of protection, if active.

Answer: The patient ate fully cooked meals and did not ingest any fresh or unpurified water. He had no exposures to domestic or wild animals. He had no sexual contacts.

Q2: Did the patient receive any pretravel vaccinations or take any prophylactic medications?

Rationale for question: Determining protective factors against infection such as vaccinations and prophylaxis helps adjust the pretest probabilities for particular infections. In general, it is recommended that individuals traveling to Cambodia receive vaccination for the following: hepatitis A (if nonimmune), Japanese encephalitis, and typhoid fever.[3] In addition, malaria chemoprophylaxis is recommended during travel to some regions of Cambodia where the prevalence of infection is high.[3] The Global TravEpiNet interactive site (https://gten.travel/prep) is a resource for determining appropriate travel vaccinations and prophylaxis.

Answer: No, the patient did not receive any vaccinations or chemoprophylaxis before this trip. He had been vaccinated for typhoid and yellow fever before his last trip to Cambodia approximately 6 years earlier.

Q3: Did the patient obtain refills for his home medications after running out?

Rationale for question: Abrupt cessation of some medications, including dopamine agonists and benzodiazepines, can precipitate withdrawal syndromes that may explain his symptoms in part or in full.

Answer: No, the patient did not have access to medication refills; in addition, he did not start any new medications while abroad.

PHYSICAL EXAMINATION

The patient's vital signs are shown in Box 2.

Box 2: Vital Signs

Temperature: 103.1°F (rectal); heart rate: 119 beats per minute; blood pressure: 159/113 mm Hg; respiratory rate: 32 breaths per minute; and O_2 saturation: 95% breathing ambient air

The patient appeared markedly diaphoretic. His mucous membranes were dry, his neck was supple, and his knee could be extended fully with his hip flexed to 90 degrees (negative Kernig's sign). Examination of the lungs revealed no adventitious sounds; his heart rhythm was regular and without murmur. No rashes or petechiae were seen. The neurologic examination revealed diffuse rigidity, tremulousness, disorientation, and dysarthria. The patient followed one-step commands, including opening his eyes, squeezing hands, looking left, and looking right. He demonstrated intact upper-extremity movements, although lower-extremity movements were not observed. There was no pronator drift. Deep tendon reflexes were normal and without clonus.

Part 2: Building the Differential Diagnosis

This patient's clinical syndrome has a number of salient features, including his history of Parkinson's disease, his recent travel to Cambodia, and notable signs and symptoms of fever, altered mental status, transient shaking movements, and diffuse rigidity. Given the prominence of his fever and altered mental status, these findings will form the foundation of the differential diagnosis. To ensure a comprehensive evaluation, potential etiologies will be categorized into three domains: infectious causes acquired during travel, infectious causes from exposures unrelated to travel, and noninfectious causes. This framework with an initial differential diagnosis is depicted in Box 3.

Box 3: Framework for Approaching the Differential Diagnosis

Infectious causes of fever and altered mental status acquired during travel: Infections that can be acquired in specific locations can be identified by utilizing resources that include information about travel-related pathogens in various geographic regions, their incubation periods, and their associated clinical syndromes.[1] The differential diagnosis in this case has to account for infections that would have been acquired in Cambodia within a 6-week timeframe. Potential causative infections include those that cause systemic illnesses associated with delirium, such as malaria, typhoid fever, melioidosis, *(continued)*

(Box 3 continued)
leptospirosis, scrub typhus, dengue fever, Zika virus, and chikungunya. In addition, central nervous system (CNS)–specific infections to consider would be viral encephalitides — particularly Japanese encephalitis virus — which can begin with a flaccid paralysis (recall here the patient's history of "slowed movements") and evolve into an encephalitis, and angiostrongyliasis, which would cause an eosinophilic meningitis.

Infectious causes of fever and altered mental status unrelated to travel: CNS-specific infections such as bacterial meningitis (e.g., caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, or *Listeria monocytogenes*), brain abscess, fungal meningitis (e.g., caused by cryptococcus), and viral encephalitides (e.g., caused by herpes simplex virus [HSV], lymphocytic choriomeningitis virus [LCMV], enterovirus, Eastern Equine encephalitis [EEE] virus, or West Nile virus [WNV]) should be considered. In addition, common bacterial infections such as pneumonia, urinary tract infections, and gastroenteritis should be considered, noting that such illnesses can lead to subacute worsening of Parkinson's disease motor symptoms.[4]

Noninfectious causes of fever and altered mental status: In this case, the concurrent hyperthermia and rigidity prompts consideration for neuroleptic malignant syndrome (NMS), although the patient is not prescribed any antipsychotic or antiemetic medications typically associated with this syndrome. Neuroleptic malignant-like syndrome (NMLS) is an entity with signs and/or symptoms similar to those of NMS that develops in the setting of withdrawal of dopamine agonist therapy. Serotonin syndrome can also present with altered mental status and autonomic dysfunction including tremor and hyperthermia, although we would expect hyperreflexia rather than rigidity, and the patient is not taking any serotonergic medications. Malignant hyperthermia from heat or vigorous exercise is another consideration, although there is no clear history of these stressors. Finally, fever can accompany CNS hemorrhage (e.g., in the brainstem or basal ganglia)[5] and severe endocrinopathies such as overt hyperthyroidism.

WHAT ADDITIONAL TESTS SHOULD BE PERFORMED?

Routine laboratory testing to investigate blood cell counts, electrolytes, and liver function will help refine the clinical syndrome and provide information about disease severity. Cultures of the blood should be obtained to assess for bacteremia. Given the increased prevalence of malaria among returning travelers who have not received chemoprophylaxis, a rapid antigen test and a thick and thin Giemsa smear examination for parasites should be performed. The combination of fever and altered mental status also necessitates a lumbar puncture. Prior to this procedure, a computed tomography (CT) scan of the head is indicated to exonerate a mass-occupying lesion. Once the lumbar puncture is performed, the cerebrospinal fluid (CSF) should be sent for the following tests: cell count and differential, protein and glucose levels, Gram stain and bacterial culture, cryptococcal antigen, and HSV polymerase chain reaction (PCR). Any residual CSF should be frozen and stored to allow for additional testing that may be indicated pending preliminary results (e.g., for arbovirus serologies or PCR).

SHOULD EMPIRICAL TREATMENTS BE STARTED?

While diagnostic evaluation is ongoing, empirical treatment for bacterial and viral meningitis and/or encephalitis should be initiated. Practice guidelines from the Infectious Diseases Society of America provide guidance on appropriate regimens.[6,7]

RESULTS

The results of all imaging and laboratory studies are shown in Box 4.

Box 4: Imaging and Laboratory Studies

Imaging

The chest radiograph (Fig. 1) demonstrated clear lungs and no effusions. A CT scan of the head without contrast (Fig. 2) showed nonspecific, mild, scattered hypodensities and generalized parenchymal volume loss.

Laboratory Results

The patient's laboratory results are shown in Figure 3.

Part 3: Refining the Differential Diagnosis

The minimal pyuria and lack of abnormal pulmonary opacities decrease suspicion for a urinary tract infection or pneumonia, respectively. Cytopenias and/or hepatic enzyme or bilirubin abnormalities, which often accompany dengue fever, Zika virus, chikungunya, and rickettsial infections, were not observed. Although the rapid malaria antigen test result is negative, malaria should remain on the differential until the definitive parasite smear is performed. The minimal CSF pleocytosis decreases suspicion for bacterial meningitis (even as the culture is pending), and the cell differential exonerates eosinophilic meningitis; however, encephalitis and other systemic infections remain on the differential. The elevated creatinine kinase (CK) and dipstick hematuria is suggestive of rhabdomyolysis, which could be attributable to hyperthermia and exertional muscle stress such as that from malignant hyperthermia, NMS, or NMLS, or associated with infections such as HSV or typhoid fever.[8] The elevated serum creatinine and azotemia could be a complication of rhabdomyolysis. Results of a CT scan of the head revealed no large hemorrhagic stroke, although smaller bleeding events could not be excluded. The normal thyroid-stimulating hormone level makes hyperthyroidism unlikely. On the basis of these results, several entities can be removed from the differential diagnosis, as shown in Box 5.

Box 5: Refining the Differential Diagnosis

Infectious causes of fever and altered mental status acquired during travel: malaria, typhoid fever, leptospirosis, melioidosis, scrub typhus, dengue fever, Zika virus, chikungunya, or viral encephalitides (e.g., Japanese encephalitis virus), ~~angiostrongyliasis~~.

Infectious causes of fever and altered mental status unrelated to travel: viral encephalitides (e.g., from HSV, LCMV, enterovirus, EEE virus, or WNV), or bacterial meningitis, ~~pneumonia, urinary tract infections, gastroenteritis~~.

Noninfectious causes of fever and altered mental status: NMS, NMLS, serotonin syndrome, malignant hyperthermia, or CNS hemorrhage, ~~overt hyperthyroidism~~.

HOSPITAL COURSE 1

Empirical intravenous vancomycin, ceftriaxone, ampicillin, and acyclovir were initiated. Despite this, the patient was persistently febrile and subsequently developed increased confusion, diaphoresis, tremulousness, and new fecal incontinence. Acetaminophen was administered, and ice packs were placed on the patient's neck, axillae, and groin for antipyresis. Rhythmic jerking movements of the arms and legs subsequently developed. His trachea was intubated for airway protection, and the patient was given propofol and midazolam for sedation and admitted to the medical intensive care unit (ICU).

HOW DOES THE INTERVAL HISTORY AFFECT YOUR APPROACH TO THE CASE?

Given the witnessed rhythmic movements, an electroencephalogram should be obtained to evaluate for epileptiform activity. Higher-resolution neuroimaging — such as magnetic resonance imaging (MRI) — is also prudent for a more sensitive evaluation for findings suggestive of CNS hemorrhage or viral encephalitis. Dual β-lactam therapy (in this case, ceftriaxone and ampicillin) can be associated with neurotoxicity and a reduced seizure threshold; as such, a drug effect should be considered as a possible contributor to the observed clinical progression.

HOSPITAL COURSE 2

An electroencephalogram effectively captured episodes of rhythmic movements, and no concurrent epileptiform activity was identified. MRI with angiography of the brain and neck demonstrated no evidence of acute infarction, intracranial hemorrhage, intracranial mass lesion, or brain abscess; in addition, no temporal or orbitofrontal lobe edema, thalamic hyperintensities, or focal regions of gadolinium enhancement consistent with viral encephalitis were seen.[9]

Additional microbiology results also returned. Cultures of the blood and urine showed no growth. Culture of the CSF showed no growth, and CSF tests for HSV type 1, HSV type 2, and cryptococcal antigen were negative. Thick and thin Giemsa smears showed no parasites, and serologic testing for dengue virus revealed a negative immunoglobulin M (IgM) and positive immunoglobulin G (IgG) result. Serologic testing for chikungunya virus likewise revealed a negative IgM and positive IgG result.

REFINING THE DIFFERENTIAL DIAGNOSIS: WHAT DO WE LEARN FROM THIS ADDITIONAL INFORMATION?

Culture- and serology-based evaluation did not reveal a culprit infection, with tests negative for bacteremia, malaria, acute dengue fever or chikungunya virus, and bacterial or viral meningitis. In addition, MRI findings were not suggestive of viral encephalitis. As such, it would be prudent to begin antimicrobial de-escalation and more closely examine causes in the "noninfectious causes of fever and altered mental status" category for the diagnosis, as shown in Box 6.

Box 6: Making a Diagnosis

Noninfectious causes of fever and altered mental status: Given the lack of triggers and/or consistent clinical syndrome ~~for NMS, serotonin syndrome or malignant hyperthermia, and no CNS hemorrhage on imaging~~, these are unlikely etiologies for the patient's presentation. Recalling that he had not taken his carbidopa-levodopa for 10 days and thus experienced abrupt cessation of dopamine agonist therapy, the most likely diagnosis here is NMLS.

~~*Infectious causes of fever and altered mental status acquired during travel*~~

~~*Infectious causes of fever and altered mental status unrelated to travel*~~

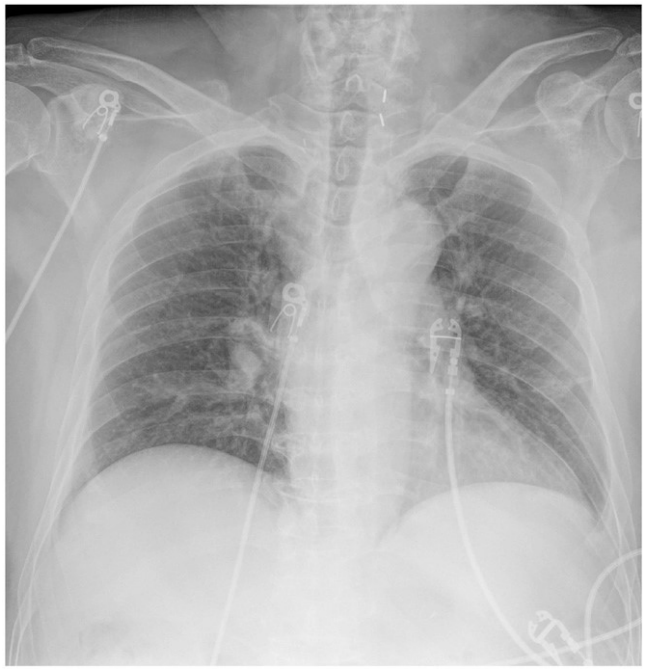

Figure 1. Chest Radiograph.

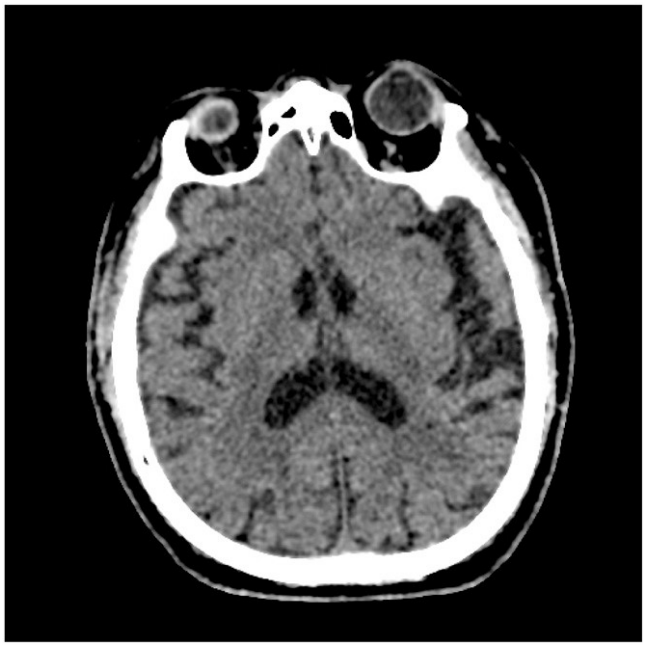

Figure 2. Computed Tomography Scan of the Head without Contrast.

HOSPITAL COURSE 3

Given the high index of suspicion for NMLS, dantrolene was administered. The patient's fever, tachycardia, and hypertension resolved within hours. Enteral access was obtained in the ICU, and his Parkinson's medications were reinitiated. No further episodes of rigidity or rhythmic movements were seen, and the CK decreased to the normal range within 48 hours. All antimicrobial agents were discontinued.

The patient was extubated and transferred out of the ICU on hospital day 3 and was discharged from the hospital on day 5. He was seen in the neurology clinic 4 weeks later, at which time he had returned to his baseline motor and cognitive function.

FINAL DIAGNOSIS

The final diagnosis was NMLS. The patient exhibited a compatible clinical syndrome with hyperthermia, rigidity, altered mental status, and sympathetic nervous system lability (tachycardia, tachypnea, diaphoresis) in the setting of dopamine agonist withdrawal.[10] In addition, an evaluation for alternative causes of this clinical syndrome, including infectious, toxic, metabolic, and neurologic causes, was unrevealing. Management of NMLS is largely supportive, including fluid administration (to replete substantial losses from fever and diaphoresis), alongside the initiation of dopamine agonist therapy.[11] There may also be roles for concurrent dantrolene for the management of hyperthermia and benzodiazepine use (for sympathetic nervous system modulation).[11]

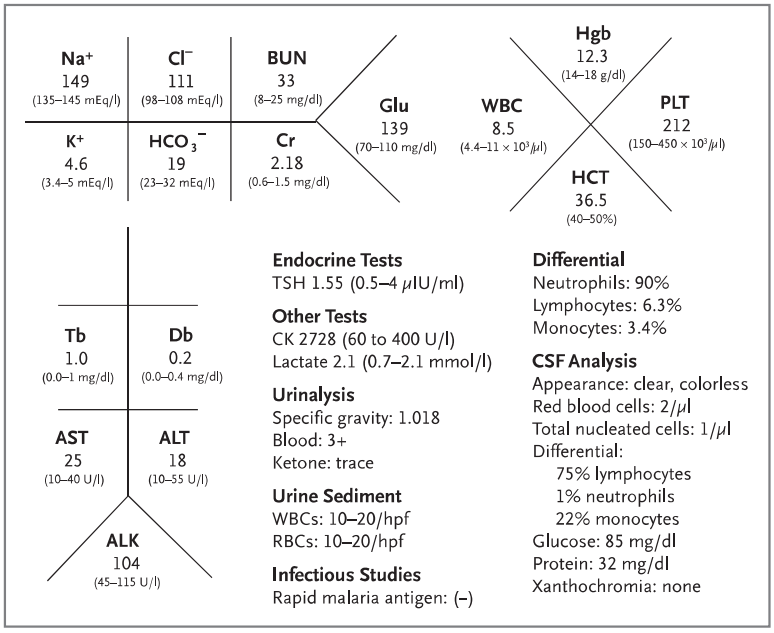

Figure 3. The Patient's Laboratory Results.

Reference ranges are given in parentheses. ALK denotes alkaline phosphatase, ALT alanine aminotransferase, AST aspartate aminotransferase, BUN blood urea nitrogen, CK creatinine kinase, Cl^- chloride, Cr creatinine, CSF cerebrospinal fluid, Db direct bilirubin, Glu glucose, HCO_3^- bicarbonate, HCT hematocrit, Hgb hemoglobin, K^+ potassium, Na^+ sodium, PLT platelet, RBC red blood cell, Tb total bilirubin, TSH thyroid-stimulating hormone, and WBC white blood cell.

TAKE-HOME POINTS

- Dopamine agonist withdrawal in the setting of Parkinson's disease can precipitate a syndrome that is clinically indistinguishable from NMS, often called NMLS.
- Complete and abrupt cessation of established anti-Parkinson's medication in a patient with Parkinson's disease should almost always be avoided. Patients who are traveling should anticipate medication needs and ensure they have enough for their trip, including potential delays in their return.
- NMLS is a neurologic emergency and should be treated with prompt resumption of dopaminergic agonists and supportive care.
- Pretravel clinical consultation is recommended to ensure appropriate vaccination and chemoprophylaxis.

Disclosures

Disclosure forms provided by the authors are available with the full text of this article at evidence.nejm.org.

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