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Fever, Rash, and Severe Arthralgias in Travelers Returning from India

CASE REPORT

By Sheela Shenoi, MD, and Albert Shaw, MD
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Dr. Shaw reports no financial relationships relevant to this field of study. Dr. Shenoi reports no financial relationship relevant to this field of study.

A 56-YEAR-OLD MAN, ORIGINALLY FROM INDIA AND WITH A HISTORY OF hypertension, had developed bilateral red, swollen ankles while on a recent trip to Bangalore. Five days later, the patient developed severe fever and shaking chills that resolved within 48 hrs. He had stayed in his brother-in-law's house in an urban setting, with several children residing there. He had not been swimming or spent any time in rural areas or farmland, nor had he been in direct contact with animals. He saw a physician, was told that he had a viral syndrome, but was given an unknown antibiotic and pain medication. Two days later, he developed diarrhea with 5 loose bowel movements, with no blood or abdominal pain, so he stopped the antibiotics with resolution of the diarrhea. He arrived back in the United States, and 24 hrs later noticed worsening of the ankle swelling, dizziness, and "red dots" on the upper extremities, prompting emergency evaluation. He reported swelling of fingers in both hands, fatigue and mild discomfort in both ankles, but was otherwise asymptomatic. The patient reported numerous mosquito bites, but took no antimalarial prophylaxis. Of note, the patient's brother-in-law in India had also developed similar symptoms.

In the hospital, the patient was afebrile and examination was significant for peripheral edema 1/3 up the calves with associated erythema and mild tenderness, without effusion or warmth. On the hands, there was mild proximal interphalangeal joint swelling bilaterally without warmth, effusion, or synovial hypertrophy. The heart and lung sounds were within normal limits, and abdominal exam was unremarkable and without hepatosplenomegaly. There was no cervical, axillary, or inguinal lymphadenopathy, and the rash had resolved.

White blood cell count was 3,600 cells /uL with 41% segmented neutrophils, 34% lymphocytes, and 10% eosinophils. Platelets were 151,000/uL with normal hemoglobin. Peripheral blood smears were negative for malaria; urinalysis was unremarkable, and blood cultures were negative. Serum creatine phosphokinase (CK) was elevated at 357 IU with normal serum CK-MB and troponin levels. AST was elevated 70 U/L and ALT was 77 U/L (nl. for both 0 - 35 U/L) with normal serum bilirubin and alkaline phosphatase.

The presumptive diagnosis was chikungunya versus dengue virus infection. The patient was discharged home. At a follow up appointment ~10 days later, the patient reported persistent arthralgias in the ankles without effusion on exam. Fourteen days after discharge, serologies sent to CDC were reported as IgM-positive, IgG-

negative for chikungunya virus and IgM-negative, IgG-positive for dengue.

COMMENTARY

The CDC's website (http://www.cdc.gov/travel/), as well as sites such as the WHO Weekly Epidemiological Record (www.who.int/wer/en/) and ProMED mail (http://www.promedmail.org/pls/promed/) are useful resources. In this case, a relevant outbreak of chikungunya virus involving > 200,000 cases starting early 2005 and peaking in December 2005 had been noted in Reunion (Indian Ocean) with associated cases in Mauritius and Seychelles. More than 340 cases have been documented in France among tourists returning from islands in the Indian Ocean. Cases have also been reported in returning travelers in China and Germany. There have been 12 cases among travelers to the United States, diagnosed serologically at the CDC in 2005-2006. In India, since March 2006, there has been an epidemic of chikungunya virus, with thousands of cases reported in the central states of Maharashtra (home to Mumbai, or Bombay), Andrha Pradesh (home to Hyderabad), and Karnataka (home to Bangalore — where our patient resided during his trip).

The local name "Chikungunya," a Makonde term meaning "that which bends up," was given in reference to the joint pain and contortions associated with severe infections. A classic paper by Robinson et al (1955) described the illness among 115 patients along the border of modern day Tanzania and Mozambique. Since then, it has been considered responsible for multiple epidemics in Africa, southeast Asia, and the Philippines, such as in Peace Corps volunteers in 1986. Retrospective studies attribute many epidemics of fever, rash, and arthralgias from Indonesia (1779) to east Africa, to India, and possibly even to the southwestern United States (1827) to chikungunya infections.

Epidemiological studies done by Robinson, Ross, and Lumsden (1955) during chikungunya outbreaks in Uganda that examined the various mosquito species in an infected village and viral infectivity demonstrated that the most likely vector was the *Aedes aegypti* mosquito, an aggressive daytime feeding species. In recent outbreaks (2/06) among the islands of the Indian Ocean, the vector is *Aedes albopictus* (the Asian tiger mosquito). Serologic studies indicate that > 20% of people in various regions of tropical Africa have evidence of infection. Clinical similarity to dengue may represent under diagnosis and underreporting of chikungunya infections.

Among the alphaviruses, chikungunya is antigenically distinct from the encephalitis viruses, WEE, EEE, and VEE, and is grouped in the Semliki Forest virus antigenic complex.

Chikungunya infections may be asymptomatic, or may appear as an abrupt illness similar in presentation to dengue infection, with fever, headache, myalgias, malaise, and severe polyarticular arthralgias, especially of the small joints and also of those which have been previously injured. Incubation period is 1-8 days. The joints become swollen, without significant effusions, and usually resolve within 1-2 weeks. Often a maculopapular rash erupts over the face and neck in the first few days of the illness, and may later reappear on the trunk, limbs, face, palms, and soles. Petechial lesions have also been frequently reported, though their pathogenesis is unclear. Lymphadenopathy is mild or absent. Conjunctivitis is frequently reported. Rare but serious CNS manifestations such

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as seizures, and meningoencephalitis have been reported, particularly in children. The acute fevers usually resolve within 3 days, though low-grade temperatures may recur later in the course. *Arthritis is frequently the most prominent symptom, and has been characterized as a symmetric polyarthritis that may affect the MCP joints, wrists, elbows, knees, ankles and MTP joints.*

The differential diagnosis includes non-hemorrhagic dengue, which is often clinically indistinguishable from chikungunya virus infections. Dengue usually has less rash, headache and arthralgia, but more adenopathy, especially long term. There are several additional arboviruses that can cause fever and arthralgias, including O'nyong-nyong which is antigenically closely related to chikungunya, but is found primarily in Africa.

Laboratory studies reveal relative leukopenia with lymphocytosis, mild thrombocytopenia, and slightly elevated ESR/CRP. A mild elevation in hepatocellular enzymes is often found. As the level of viremia and fever trend down, hemagglutinin inhibition and serum antibodies rise. An antibody capture IgM ELISA is available through CDC (CDC Arboviral Diseases Branch: 970-221-6400; instructions for shipping specimens: www.cdc.gov /ncidod/dvbid/misc/specimen-submission.htm). A reverse transcription PCR (E1 protein and non-structural protein 1) has been developed which takes less than 48 hours but is not widely available in the United States. Generally, diagnosis is made on clinically grounds.

Many patients recover uneventfully with supportive care, including rest, hydration, acetaminophen and/or NSAIDS. However, arthritis may be persistent and occasionally incapacitating in adults; 4 months later, up to 50% may have musculoskeletal findings such as morning stiffness, decreased grip strength, tenosynovitis, and periarticular soft tissue swelling, especially involving the proximal interphalangeal joints (Kennedy et al, 1980). Of the 4 patients presented in the CDC case series, one patient's arthralgias persisted for approximately one month, whereas another patient's joint symptoms persisted for up to 5 months. Cardiac involvement, including arrhythmias or cardiomyopathy and heart failure, has been rarely suggested to be associated with chikungunya infections. The development of a live-attenuated vaccine in a phase II trial has been reported, though it is still in trial.

As *Aedes albopictus*, the chikungunya vector in the Indian Ocean outbreak, is prevalent worldwide, including the Americas, there is risk that infected returning travelers may introduce chikungunya into local mosquito populations and cause outbreaks, especially in temperate areas of the United States. Patients with suspicion for infection should be reported and should avoid introduction of the virus to local mosquitoes by staying indoors as much as possible, wearing long sleeves, and using insect repellents during the first week of illness. ■

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Update on Guillain-Barré Syndrome and Menactra® Meningococcal Conjugate Vaccine

ABSTRACT AND COMMENTARY

By Mary-Louise Scully, MD

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Dr. Scully reports no financial relationships relevant to this field of study.

Synopsis: *This report summarizes the 9 additional reports of Guillain-Barré Syndrome to the Vaccine Adverse Event Reporting System (VAERS) during March through September 2006. There have now been a total of 17 cases. Although the available data suggest a small increased risk for Guillain-Barré Syndrome after Menactra® Meningococcal Conjugate Vaccine (MCV4), the CDC recommends continuing routine vaccination of adolescents, college freshman living in dormitories, and persons increased risk of meningococcal disease.*

Source: CDC. Update: Guillain-Barré Syndrome Among Recipients of Menactra® Meningococcal Conjugate Vaccine-United States, June 2005- September 2006. *MMWR Morb Mortal Wkly Rep*.2006; 55:1120-1124.

In October of 2005, the first reports of 5 cases and the possible association of Guillain-Barré

Syndrome (GBS) and recipients of Menactra® Meningococcal Conjugate Vaccine (MCV4) were reported. In April 2006, 3 additional confirmed cases of GBS within 6 weeks of MCV4 vaccination were reported. This most recent report summarizes 9 additional cases, resulting in a total of 17 GBS cases reported since June of 2005.

Of the 9 new cases, 5 were male and 4 were females. All but 2 patients (ages 43 and 30) were between the ages of 15 to 18. Each of the 9 cases was reviewed by both a CDC medical officer and a clinical investigator from Boston University. Four of the 9 had received MCV4 as the sole vaccination. The other patients had received concurrent vaccines such as Hepatitis A, Hepatitis B, Tdap, and human papillomavirus (HPV) vaccine. One patient, the 43-year-old male, received 6 other concomitant vaccinations with MCV4, including trivalent inactivated influenza vaccine. The range of onset of the adverse event from vaccination with MCV4 was 2-33 days with a mean of 15.7 days. The timing and onset of neurological symptoms after MCV4 vaccination is of concern.

Using data from the Healthcare Cost and Utilization Project (HCUP) and the Vaccine Safety Datalink (VSD), the background incidence rate for GBS among patients aged 11-19 years was estimated at 0.11 per 100,000 person-months. The rate of GBS was estimated to be 0.20 per 100,000 person-months in 11-19 year olds who had received MCV4. However, in a separate VSD analysis, a total of 126,506 doses of MCV4 were delivered between March 2005 and September 2006, and no cases within 6 weeks of vaccination were observed in recipients aged 11-19 years (0.2 cases would have been expected). Two cases of GBS were reported among an equal number of 11- to 19-year-olds receiving preventive care who had not received MCV4 vaccination.

Campylobacter jejuni, a cause of bacterial gastroenteritis, is a known precipitating factor for GBS. It is unlikely that *C. jejuni* played a role in these recent reports.

COMMENTARY

Menactra®, a quadrivalent (A, C, Y, and W135) meningococcal conjugate vaccine (MCV4), was licensed in the United States on January 14, 2005. Each 0.5-ml dose of MCV4 contains 4 µg each of capsular polysaccharide from *Neisseria meningitidis* serogroups A, C, Y, and W135 conjugated to 48 g of diphtheria toxoid. The MCV4 vaccine is approved for ages 11 to 55 years old. In February of 2005, the Advisory Committee on Immunization Practices (ACIP) recommended that in addition to the previous recommendations for first year college students living in dormitories and other high risk groups, MCV4 be given at the preadolescent visit (ages 11-12 years) or prior to high school at 15 years if not previously vaccinated.[1]

The serogroups responsible for most cases in the United States are serogroups B, C, and Y. No vaccines for serogroup B are readily available except in New Zealand. Serogroup B accounts for a significant amount of disease in Europe and America and often occurs in infants, a group at high risk of invasive disease and little immunologic maturity.[2] In the meningitis belt of sub-Saharan Africa, epidemics secondary to serogroup A and more recently W-135 predominate. In the United Kingdom, high rates of serogroup C led to a campaign to immunize all infants and children with a serogroup C conjugate vaccine.

Unfortunately, it may take several years of monitoring to more clearly define the risk association of GBS and MCV4. In May of 2006, in response to a vaccine shortage of MCV4, the CDC and the Advisory Committee on Immunization Practices (ACIP) recommended deferral of vaccination of children aged 11 to 12 years. These vaccine shortages have now been resolved and as of November 3, 2006, the routine vaccination of children 11 to 12 years old should resume.[3] Further monitoring will be essential as we resume full-scale vaccination of these adolescents.

An updated fact sheet for health care workers on GBS and Menactra is available at www.cdc.gov/nip/vacsafe/concerns/gbs/Menactra.htm. Patients with prior history of GBS should not receive MCV4. Any provider who suspects GBS or any other adverse event after MCV4 is encouraged to report online at www.vaers.hhs.gov or by fax at 877-721-0366. ■

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2. Harrison L. Vaccine Prevention of Meningococcal Disease: Making Slow Progress. *Clin Infect Dis*. 2006; 43:1395-1397.
3. CDC. Notice to Readers: Improved Supply of Meningococcal Conjugate Vaccine, Recommendation to Resume Vaccination of Children 11-12 Years. *MMWR* 2006; 55(43):1177-1178.

CME Objectives

- To present the latest data regarding the diagnosis and treatment of various travel-related diseases;
- To present new data concerning recommended precautions and prophylaxis for patients traveling to specific areas of the world; and
- To alert the readers to recent disease outbreaks and epidemics. ■

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Study: Long-Term Use of Clopidogrel for DES Patients

Patients with coronary artery disease who have received intra-coronary, drug-eluding stents (DES) may benefit from longer courses of clopidogrel than is currently standard. Researchers at Duke looked at 4,666 patients undergoing percutaneous coronary interventions with bare metal stents (BMS) (n = 365) or DES (n = 1501). Patients were followed up at 6, 12, and 24 months with the main outcomes being death, non-fatal MI, and the composite of death or MI at 24-month follow-up. For patients who received DES and were event free at 6 months, use of clopidogrel was a significant predictor of fewer events at 24 months (death rate 2.0% with clopidogrel vs 5.3% without , P = 0.3; death/MI 3.1% vs 7.2%, P = 0.02). However the same was not seen for BMS patients, with no significant difference in death rate or death/MI in the patients who took clopidogrel. For DES patients who were event free at 12 months, use of clopidogrel continued to improve outcomes (death rate 0% with clopidogrel versus 3.5% without, P = .004; death/MI 0% versus 4.5%, $P <$ 0.001). For patients with BMS who were event free at 12 months, use of clopidogrel was still not associated with any change in death rate (3.3% vs 2.7% P = 0.57) or death/MI (4.7% 3.6%, P = 0.44). The authors conclude that extended use of clopidogrel in patients with drug-eluding stents may reduce the rate of death and MI. However the appropriate duration of clopidogrel administration has not yet been determined. (*JAMA* early release article posted 12/05/06). Implications of the study are significant in that current recommendations following PCI with drug eluting stents is for 3 to 6 months of clopidogrel. Several studies have shown that these stents have increase risk of catastrophic stent thrombosis, higher than bare metal stents, months after the procedure. This has led some experts to recommend long-term use of clopidogrel, perhaps even lifetime use in patients who have received a DES. While the study does not make recommendations, it does confirm the fact that clopidogrel is beneficial for patients who received a DES for up to 2 years.

Drug Labels — A Prescription for Misunderstanding?

Prescription drug labels are commonly misunderstood according to a new study in the *Annals of Internal Medicine*. Nearly 400 English-speaking patients were enrolled in the study to assess their understanding of 5 different medication labels, all had relatively common instructions. Patients with low literacy, defined as 6th-grade level or less, were less likely to understand all 5 labels. Patients with low literacy read the instruction, "Take two tablets by mouth twice daily," but only 35% could demonstrate the number of pills to be taken daily. Patients who had multiple prescriptions were significantly

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: jennifer.corbett@ahcmedia.com.

more likely to misunderstand prescription labels. The authors admit that the patient's actual drug-taking behaviors were not observed, so authors could not demonstrate a link between misunderstanding the labels and actual medication errors. Still the authors suggest that patients of all ages would benefit from additional efforts to improve the clarity of prescription labels and suggest that the text and format of existing prescription containers should be redesigned and standardized (*Ann Int Med*. 2006;145: Epub ahead of print).

Osteonecrosis of the Jaw — New Side-Effect to Bisphosphate Use

With the widespread use of bisphosphonates for the prevention and treatment of osteoporosis, a new side effect, osteonecrosis of the jaw, has emerged as a concern. A new "Perspective" piece in the *New England Journal of Medicine* (November 30) helps answer the question, "Osteonecrosis of the Jaw—Do Bisphosphonates Pose a Risk?" Osteonecrosis of the jaw is characterized by exposed bone in the mandible, maxilla, or palate, and is often associated with dental disease, dental surgery, oral trauma, periodontitis, and poor dental hygiene. The author points out that the first case of osteonecrosis associated with bisphosphonates was reported in 2003, nearly 10 years after the drugs were first approved. Most reported cases are associated with high-dose intravenous bisphosphonates given to control metastatic bone disease where the rate is reported from 1.3% to 7%. The average patient with osteonecrosis had been receiving intravenous bisphosphonate therapy for 1.5 to 3 years. Use of oral bisphosphonates to treat osteoporosis involves doses that are often 10 times lower than intravenous doses. Fewer than 50 cases of osteonecrosis of the jaw have been associated with oral bisphosphonates, or approximately 1 in 100,000 patient years. There is concern that with long-term use of oral bisphosphonates, the rate of osteonecrosis may increase in the future. Some have even suggested that osteoporosis patients take a "drug holiday" after 5 years of therapy to reduce the risk; however, the benefit of the strategy is unclear at this time. A routine dental evaluation is reasonable prior to starting bisphosphonates; however, there is no reason to stop the drugs prior to dental treatment. Some oral surgeons advocate temporarily withholding drugs if invasive dental care is needed, but given the very long half-life of these drugs, it is unclear whether temporary cessation will have any effect on reducing the risk of osteonecrosis, and more research is needed (*N Eng J Med*. 2006; 355:2278-2281).

Beta-Blockers and Depression — Unlinked?

Many physicians are cautious about the use of beta-blockers after myocardial infarction because of the risk of depression. A new study suggests that this concern may be unwarranted. Researchers from the Netherlands looked at 127 patients who had a myocardial infarction and were not taking beta-blockers versus 254 MI patients who were taking beta-blockers at 3, 6, and 12 months post MI. Outcomes were scores on 2 commonly used depression scales. No significant differences were found between beta-blocker users and non-beta-blocker users regarding the presence of depressive symptoms or depressive disorder, although a trend towards more depression was seen in patients with long-term use of beta-blockers and patients on higher doses. Use of a hydrophilic versus lipophilic beta blocker made no significant difference. The authors conclude that in post MI patients, use of beta-blockers is not associated with an increase in depressive symptoms or depressive disorders in the first year (*J Am Coll Cardio*. 2006;48:2209-2214).

FDA Actions

The FDA has approved telbivudine for the treatment of chronic hepatitis B virus (HBV) infections in adults. The drug is approved for patients with evidence of viral complication in either persistent elevations in serum transaminases or histologically active disease. The approval was based on a one-year study, and more than 1,300 patients showed significant decreases in HBV-virus DNA levels compared with lamivudine. Telbivudine, which is given as a 600 mg oral daily dose, will be marketed by Idenix Pharmaceuticals and Novartis as "Tyzeka."

FDA has approved the first generic version of ondansetron injection (Zofran) for the prevention of nausea and vomiting associated with chemotherapy and prevention of postoperative nausea and vomiting. The generic product will be manufactured by Teva and SICOR Pharmaceuticals. GlaxoSmithKline, which previously held the patent for Zofran, had 2005 sales of nearly $850 million.

The FDA has approved expanded use of Herceptin for HER2-positive, early-stage breast cancer after mastectomy or lumpectomy. Previously, the drug was only approved for HER2-positive, metastatic breast cancer. ■