Research Paper

Rhabdomyolysis in Patients with West Nile Encephalitis and Meningitis

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ABSTRACT

Since 1999, more than 6,500 cases of West Nile virus neuroinvasive disease (WNND) have been reported in the United States. Patients with WNND can present with muscle weakness that is often assumed to be of neurologic origin. During 2002, nearly 3,000 persons with WNV meningitis or encephalitis (or both) were reported in the United States; in suburban Cook County, Illinois, with 244 persons were hospitalized for WNV illnesses. The objective of this investigation was to describe the clinical and epidemiological features of identified cases of WNV neuroinvasive disease and rhabdomyolysis. Public health officials investigated patients hospitalized in Cook County, and identified a subset of WNV neuroinvasive disease patients with elevated creatine kinase levels. Cases were defined as hospitalized persons with a WNV infection, encephalitis or meningitis, and rhabdomyolysis. Retrospective medical record reviews were conducted and data was abstracted with a standardized data collection instrument. Eight patients with West Nile encephalitis and one with West Nile meningitis were identified with rhabdomyolysis. Median age of the nine patients was 70 years (range, 45–85 years), and eight were men. For all nine patients, the peak CK level was documented a median of 2 days after hospitalization (range, 1–24 days). Median CK level during hospitalization for all case-patients was 3,037 IU (range, 1,153–42,113 IU). Six patients had history of recent falls prior to admission. Although the temporal relationship of rhabdomyolysis and neurologic WNV illness suggested a common etiology, these patients presented with complex clinical conditions which may have led to development of rhabdomyolysis from other causes. The spectrum of WNV disease requires further investigation to describe this and other clinical conditions associated with WNV infection. Key Words: West Nile virus—Rhabdomyolysis—Encephalitis.

INTRODUCTION

Viral infections have been identified as an infrequent cause of rhabdomyolysis. Elevated creatine kinase (CK) levels have been attributed to a direct effect of viruses such as the influenza and Coxsackie viruses (Pesik and Otten 1996, Singh and Scheld 1996, Ytterberg 1996) on myocytes and to the interaction of viral infections with certain medications or physical exertion (Joshi and Liu 2000). Patients with West Nile virus (WNV) neuroinvasive disease (less than 1% of WNV-infected persons) commonly present with muscle weakness that is often assumed to be of neurologic origin. Although rhabdomyolysis has been described in WNV-infected persons with severe neurologic impairment (Kulstad and Wichter 2003, 1Arbovirus Diseases Branch, Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), Public Health Service, Department of Health and Human Services, Fort Collins, Colorado.
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Jeha et al. 2003), the mechanisms behind the elevated CK levels are unclear. In these impaired patients, rhabdomyolysis may be secondary to crush injury or muscle tissue hypoxia following falls or to physiological interactions with medications that are associated with rhabdomyolysis. Currently, direct evidence of WNV infection causing myositis has not been documented (Smith et al. 2004); however, the virus can cause muscle cell damage in vitro (Bao et al. 1992). Rare cases of WNV-associated hepatitis, pancreatitis, and myocarditis have also been reported (Georges et al. 1987, Nash et al. 2001, Platonov et al. 2001).

During 2002, nearly 3,000 persons with WNV meningitis or encephalitis (or both) were reported in the United States. In suburban Cook County, Illinois, 244 persons were hospitalized with WNV illnesses (M.J. Chudoba, personal communication). As part of epidemic-related investigations, public health officials from the Cook County Department of Public Health, Illinois Department of Public Health, and the Centers for Disease Control and Prevention (CDC) reviewed medical records of persons hospitalized with WNV illnesses. This report describes patients with WNV neuroinvasive disease and evidence of rhabdomyolysis.

MATERIALS AND METHODS

These investigations were carried out as part of public health surveillance. For this report, we have included as cases those hospitalized persons with a laboratory-confirmed WNV infection (Griffin 2000), neuroinvasive disease (encephalitis or meningitis) (Centers for Disease Control and Prevention 2001), and rhabdomyolysis defined as a CK level at least five times the upper normal limit at the testing laboratory. For patients who met these criteria, investigators completed a second, more detailed medical record abstraction, including information about past medical history and hospital course. Laboratory diagnosis of acute WNV infection was confirmed at CDC's Division of Vector-Borne Infectious Diseases (Fort Collins, CO), and at the Illinois Department of Public Health.

RESULTS

Of 14 persons with laboratory-confirmed WNV neuroinvasive disease and elevated CK levels, nine had sufficiently elevated CK levels to meet the case definition. Eight had encephalitis and one had meningitis; none had acute flaccid paralysis. Median age of the nine patients was 70 years (range, 45–85 years), and eight of the nine patients were men (Table 1). Patients were reported from six hospitals in Cook County; five hospitals yielded one patient and one hospital reported four patients. No muscle tissue was biopsied or examined for WNV infection in any of these cases.

On admission, five of the nine patients were febrile and six had generalized muscle weakness. Six patients had documented elevated CK levels on the day of admission; for two, this was the maximum CK level measured during hospitalization. For all nine patients, the peak CK level was documented a median of 2 days after hospitalization (range, 1–24 days). Median CK level during hospitalization for all case-patients was 3,037 IU (range, 1,153–42,113 IU).

Six patients had a history of a fall within three days before admission but three had no reported history of a fall, trauma, or immobilization. Two patients had been taking cholesterol-lowering statin medications. One patient had a history of alcohol abuse and was admitted for delirium tremens but was subsequently diagnosed with WNV encephalitis. Prior to hospitalization, none had taken any drugs considered as risk factors for malignant hyperthermia.

Of the three persons for whom there was no history of trauma, prolonged immobilization, or crush injury, one was taking a medication (pravastatin) that has been previously associated with rhabdomyolysis (Pasternak et al. 2002) and one, as mentioned above, had a history of alcohol abuse which has also been identified as a cause of rhabdomyolysis (Qui et al. 2004). One patient with reported trauma had a previous history of renal disease requiring dialysis and developed acute renal failure during hospitalization, requiring treatment by dialysis for two days.

Two cases are described below.
<table>
<thead>
<tr>
<th>Case number</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Illness admission date</th>
<th>Hospital admission date</th>
<th>Medications prior to admission</th>
<th>First measured CK level (IU/L) (hospital day of first level)</th>
<th>Peak CK level (IU/L) (hospital day of peak level)</th>
<th>WNV disease clinical syndrome</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>Male</td>
<td>8/17/2002</td>
<td>8/20/2002</td>
<td>Acetaminophen, bupropion, metaxalone, paroxetine, ramitidine, rofecoxib</td>
<td>Yes (fall) 112 (day 1)</td>
<td>3,037 (day 3)</td>
<td>Meningitis</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>Male</td>
<td>8/17/2002</td>
<td>8/20/2002</td>
<td>None</td>
<td>Yes (fall) 14,054 (day 1)</td>
<td>17,388 (day 2)</td>
<td>Encephalitis</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>Male</td>
<td>7/31/2002</td>
<td>8/6/2002</td>
<td>Flunisolide inhaler, levofloxacin,</td>
<td>No</td>
<td>3,205 (day 2)</td>
<td>3,205 (day 2)</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>4</td>
<td>86</td>
<td>Female</td>
<td>8/7/2002</td>
<td>8/11/2002</td>
<td>Digoxin, enalapril, metformin, tolvaterodine, famotidine, hydrochlorothiazide, ranitidine</td>
<td>Yes (fall) 106 (day 1)</td>
<td>2,270 (day 4)</td>
<td></td>
<td>Encephalitis</td>
</tr>
<tr>
<td>5</td>
<td>85</td>
<td>Male</td>
<td>8/26/2002</td>
<td>8/29/2002</td>
<td>Fennoxazole, hydrochlorothiazide, ranitidine, ramitidine</td>
<td>Yes (fall) 2,807 (day 1)</td>
<td>2,807 (day 1)</td>
<td>Encephalitis</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>Male</td>
<td>7/31/2002</td>
<td>8/5/2002</td>
<td>Aspirin, isosorbide dinitrate, pravastatin</td>
<td>No</td>
<td>1,113 (day 2)</td>
<td>1,315 (day 24)</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>7</td>
<td>46</td>
<td>Male</td>
<td>9/12/2002</td>
<td>9/18/2002</td>
<td>Nyquil® b Robitussin® c</td>
<td>No</td>
<td>209 (day 1)</td>
<td>2,782 (day 2)</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>8</td>
<td>77</td>
<td>Male</td>
<td>9/7/2002</td>
<td>9/8/2002</td>
<td>Alendronate, diphenhydramine, latanoprost (ophthalmic solution), tenaxin</td>
<td>Yes (fall) 42,113 (day 1)</td>
<td>42,113 (day 3)</td>
<td>Encephalitis</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>70</td>
<td>Male</td>
<td>8/10/2002</td>
<td>8/12/2002</td>
<td>Folic acid, glipizide, lisinopril, metformin, simvastatin</td>
<td>Yes (fall) 5,136 (day 2)</td>
<td>5,552 (day 3)</td>
<td></td>
<td>Encephalitis</td>
</tr>
</tbody>
</table>

aMyoglobin was elevated (1,375 mg/dL) on day of admission.
bProcter & Gamble, Cincinnati, Ohio.
cWyeth, Madison, New Jersey.
dCase patient 8 had an elevated CK level of 5,211 IU during an emergency room visit 1 day prior to hospitalization.
Rhabdomyolysis and West Nile Virus

Case 3

On August 6, a 70-year-old man was hospitalized with a 7-day history of balanoposthitis, fever, and chills. Temperature upon admission was 39.6°C; mental status was normal. Medical history included recurrent balanoposthitis over the past 6 months, vascular disease, hyperlipidemia, chronic obstructive pulmonary disease, and sulfa drug allergy. The patient had a protracted history of smoking. Preadmission medications included inhaled flunisolide and one dose of levofloxacin. To treat febrile illness due to balanoposthitis, broad-spectrum antibiotics (cefazolin and gentamicin) were prescribed and elective circumcision surgery was performed on day two of hospitalization under anesthesia with fentanyl and thiopental. Immediately following surgery, the patient experienced fever to 39°C and new onset atrial fibrillation. His mental status deteriorated and he developed tonic-clonic seizures and right hemiparesis as well as generalized macular rash, nuchal rigidity, and pigmenturia. Treatment with additional antibiotics (ceftriaxone, vancomycin, and clindamycin) and an antifungal (fluconazole) was initiated. With additional antibiotics, the patient developed delirium tremens. Despite multiple doses of benzodiazepines, the patient's neurological signs persisted and he was transferred to intensive care. On day 2 of hospitalization, WNV encephalitis was confirmed by the presence of pleocytosis, elevated protein, and WNV-specific IgM antibody in cerebrospinal fluid (CSF) as well as WNV neutralizing antibody in serum. On admission (day 4 of illness), the measured CK level was 209 U/L (normal range, 30–200 U/L); by day 6 of illness, the CK level had risen to 2,782 U/L. On day 8, CK decreased to 1,865 U/L. Cardiac muscle isoenzyme and troponin levels were within normal ranges, and the elevated CK was not considered consistent with an acute coronary syndrome; myocardial infarction was ruled out by the attending physician based on electrocardiogram findings. Serum creatinine and BUN levels remained normal throughout hospitalization. The patient developed respiratory arrest requiring ventilator support for 6 days, but improved and was discharged to his home with residual episodes of confusion and anxiety after 12 days of hospitalization.

DISCUSSION

Rhabdomyolysis is a syndrome characterized by elevation of serum CK and myoglobin secondary to the loss of muscle cell membrane integrity. Although clinical definitions may vary, elevated serum CK is generally accepted as the most sensitive and timely indication of rhabdomyolysis (Visweswaran and Guntupalli 1999, Bontempo 2002, David 2000, Slater and Mullins).
1998). The timing of peak CK level and elimination from the bloodstream allows for evaluation of the duration and the approximate extent of muscle damage. This muscle damage has been attributed to a wide variety of infectious and noninfectious causes (Bontempo 2002). However, the mechanisms resulting in damage to muscle cell membranes are thought to include electrolyte imbalances, ischemia, hypovolemia, hyperthermia, and metabolic derangements.

Some noninfectious causes of rhabdomyolysis include physical over-exertion, electrocution, trauma, and illicit or therapeutic drug use. Numerous classes of drugs have been implicated in the development of rhabdomyolysis, including therapeutic drugs such as the cholesterol-lowering statins, neuroleptics, antibiotics, and recreational drugs such as ethanol, cocaine, and amphetamines. Neuroleptic malignant syndrome is a rare and potentially serious reaction to neuroleptic medications characterized by fever and muscle rigidity. Antipsychotic drugs have also been reported to cause elevations in CK without concomitant myoglobinuria to indicate muscle damage (Meltzer et al. 1996).

Viral and bacterial infections have been associated with rhabdomyolysis (Pesik and Otten 1996, Singh and Scheld 1996, Ytterberg 1996). Suggested mechanisms of muscle cell damage leading to rhabdomyolysis include direct cellular invasion and the effects of toxins on the internal cellular components and processes. For influenza virus, direct viral infection of muscle cells with an overwhelming intracellular proliferation of viral particles has been hypothesized, although this has not been consistently observed (Singh and Scheld 1996). Rhabdomyolysis has been reported in patients with human immunodeficiency virus infection. Co-infection with toxin-generating pathogens such as *Staphylococcus aureus*, immune-mediated pathology associated with HIV seroconversion, and illicit drug use have been suggested as causes of rhabdomyolysis in these cases (Joshi and Liu 2000).

Reports of rhabdomyolysis in patients with flavivirus infections are rare (Kulstad and Wichter 2003, Jha et al. 2003, Gunasekera, et al. 2000, Davis and Bourke 2004). Signs and symptoms compatible with rhabdomyolysis, such as muscle weakness and/or pain, can be reported with WNV disease but CK elevations are not usually documented in association with those signs. A direct role for WNV in the development of muscle damage, either by viral proliferation within muscle cells or via immune-mediated mechanisms, has not been demonstrated.

Patients with WNV illnesses may have preexisting conditions, such as chronic alcohol abuse or the use of statins for hyperlipidemia, which increase their risk for rhabdomyolysis. In addition, WNV encephalitis patients may develop neurological conditions leading to involuntary movement disorders, trauma such as falls and to periods of immobility. Partial or complete ischemia for two or more hours has been demonstrated to produce muscle cell damage (Slater and Mullins 1998). In addition, the use of antipsychotic medications and vasoconstrictor agents during treatment of encephalitis may also lead to the development of rhabdomyolysis (Meltzer et al. 1996).

The two WNV encephalitis cases detailed in this report illustrate the complex clinical situations often encountered when WNV infection is complicated by severe neurological disease, making infection-associated rhabdomyolysis difficult to distinguish from rhabdomyolysis resulting from other causes. Neither of the two WNV encephalitis patients detailed here presented with a history of trauma. In the first case (case 3), rhabdomyolysis could have been due to anesthetic drugs or the single dose of levofloxacin. Peak elevation in circulating CK typically occurs 24 h or more after physical insult (Bontempo 2002, Slater and Mullins 1998); the short interval between onset of seizure activity and detection of elevated CK suggests that rhabdomyolysis was not a result of seizure activity in this case. The second case-patient (case 7) had no current risk factors but did have a history of alcohol abuse. History of fall was recorded in seven of the nine cases summarized here; resultant trauma and immobility may have caused reduced blood flow to affected muscle masses and rhabdomyolysis. Physicians caring for WNV neuroinvasive disease patients should be aware that these individuals may develop marked CK elevations, especially if other potential risk factors for rhabdomyolysis are present.
RHABDOMYOLYSIS AND WEST NILE VIRUS

Since the introduction of WNV to the United States in 1999, the virus has caused epidemics of neuroinvasive disease every year, affecting an increasingly large area of the country. With each epidemic, collective knowledge of the clinical spectrum of WNV disease has increased. This investigation describes patients with West Nile encephalitis and meningitis who developed rhabdomyolysis, a possible complication of WNV disease. Future epidemics will provide opportunities to investigate this and other clinical conditions associated with WNV infection in order to further define the spectrum of WNV disease.

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REFERENCES


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