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Case Report

West Nile Fever – Clinical and Epidemiological Characteristics. Review of the Literature and Contribution with Three Clinical Cases

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Abstract

West Nile fever (WNF) is a vector-borne infection caused by a *Flavivirus*-West Nile virus (WNV). WNV is transmitted by mosquitoes, and birds are the major natural reservoir. A recent increase in the number of the WNF cases has been reported in Europe, the Balkans, and Bulgaria. We herein present the clinical course, laboratory and imaging findings of three patients – a female and two male patients, who were diagnosed with WNF. They were investigated in an epidemiological study, and by using clinical observation, laboratory and microbiological methods, serological tests for specific anti-WNV antibodies detection, molecular biology techniques (polymerase chain reaction, PCR), computed tomography (CT) and magnetic resonance imaging (MRI). The patients presented with fever, headache, drowsiness, and dizziness and anti-WNV antibodies were detected in their serum samples. WNV-RNA was found in a blood sample from the female patient. Both anti-WNV IgM and Herpes simplex virus-1 DNA were detected in a cerebrospinal fluid sample from one of the men. The three patients recovered from the disease after a long convalescent period. WNF has no specific signs, laboratory and imaging findings and could be a life-threatening condition, leading to serious complications. Therefore, WNF should be taken into consideration during the summer when the vector of the infection is active.

Keywords

ataxia, dizziness, headache, fever, West Nile virus

INTRODUCTION

West Nile fever (WNF) is a vector-borne viral disease that manifests with fever, flu-like symptoms, and gastrointestinal disorders, and occasionally rash and lymphadenomegaly occur. In 1% of the cases the condition progresses to a neuroinvasive disease – the West Nile neuroinvasive disease (WNND) with clinical signs of meningitis, encephalitis and/or acute flaccid paralysis.[1-3] WNF is caused by the West Nile virus (WNV), which was first isolated from a febrile woman in West Nile Area (Uganda, Africa).[1,4,5] WNV is a member of the *Flaviviridae* family, genus *Flavivirus*. The major sources of infection are birds. WNV is transmitted to vertebrate hosts – humans and mammals by mosquitoes, predominantly from genus *Culex*. The viral circulation in the environment is maintained by a transmission cycle between the source of infection and the vector, the mosquitoes. An infection might occur after blood transfusion and organ transplantation from viremic donors.[1,6-9]

Some regions in Africa and Asia are endemic for WNF. In the 1990s, cases of WNV encephalitis were reported in Algeria, Czech Republic, France, Romania, Russia and Israel.[10] WNF outbreaks occurred in Greece (262 cases in 2010), Israel (> 200 cases in 2000), Romania (about 400

cases in 1996) and in Russia (262 cases in 1999). A large number of the affected patients developed neurologic complications that led to death in some of them.[1,2,11,12]

In 1999, WNV circulating in Israel and Tunisia was imported in the USA and spread throughout Canada and South America. WNF outbreaks occurred in the USA in 2002, 2003, and 2012. The greatest number of WNV cases was reported in 2012 - 5674 patients, 286 of whom died. WNV is classified as the major causative agent of vector-borne epidemic encephalitis in the USA.[1,12]

The incubation period is between 2 - 6 days and may extend to 14 days in *immunocompromised* persons. In about 80% of cases, WNF is an asymptomatic infection. Twenty percent of the infected individuals present with fever, arthralgia, myalgia, fatigue, malaise, headache, and retro-orbital pain. Other nonspecific symptoms include anorexia, nausea, vomiting, diarrhea, cough, and sore throat. During the epidemic outbreaks, flush, generalised lymphadenopathy, hepatomegaly and splenomegaly were also observed. One percent of the patients develop WNND with clinical signs of meningitis, encephalitis or acute flaccid paralysis. These symptoms are usually seen a few days after the onset of the disease. Two-thirds of the WNND cases manifest as encephalitis and one-thirds – as meningitis.[1]

WNV encephalitis manifests with signs unusual for other viral encephalitis such as tremor, Parkinsonism, muscle rigidity, bradykinesia and myoclonus, muscle weakness, hypotonia and areflexia, cranial neuropathy (uni- or bilateral facial nerve injury). The cerebellar abnormalities include ataxia, gait and coordination disorders.[13]

Injuries of the spinal cord lead to acute flaccid paralysis that presents with flaccid and asymmetrical paralysis, similar to that in poliomyelitis, with an acute onset and hypo- or areflexia. If the damage involves upper parts of the spinal cord, intercostal paralysis, disorders of the diaphragm function, and respiratory failure may occur. An extensive spinal cord involvement results in quadriplegia.[1,7,13]

The lethality rate of WNF is estimated to be between 3% - 15%. Patients in advanced age, those with comorbidities and immunsuppression may experience a more severe course of the disease with the development of life-threatening complications that may lead to death.[1,10] The convalescent period is rather long – it takes some months or a year. Most of the patients complain of persistent adynamia, depression, apathy and anxiety until they fully recover.[7]

The treatment of WNF includes administration of symptomatic and pathogenetic medications, depending on the clinical manifestations as there is no specific etiological treatment. Antiedematoes agents and glucocorticoids are administered in a neuroinvasive disease and mechanical ventilation is indicated in patients with respiratory failure.

Immune γ-globulin, WNV-specific neutralizing monoclonal antibodies, ribavirin, INF α-2b, and antisense oligomers are being investigated, but their therapeutic efficacy has not been confirmed in a clinical study yet because of the insufficient number of patients involved.[6-8]

Over the last ten years, 33 cases of WNF have been reported in Bulgaria according to the data of the National Centre of Infectious and Parasitic Diseases.[14-22] In 2019, three probable and 5 confirmed cases of WNF were reported.

Three WNF cases were reported in Pazardzhik district.

AIM

The aim of the study was to present the clinical course and laboratory findings of patients diagnosed with WNF.

MATERIALS AND METHODS

Patients

Three patients with WNF, who were treated at the Department of Infectious Diseases of Pazardzhik Multiprofile Hospital for Active Treatment in 2018 and 2019, were investigated in an epidemiological study, using clinical observation, laboratory tests of blood, urine and CSF, serological tests for detection of specific anti-WNV IgM and IgG antibodies, microbiological and molecular biology techniques (polymerase chain reaction, (PCR), and medical imaging studies – CT and MRI.

Clinical samples

Serum, blood and CSF samples were taken from the patients. The laboratory tests were performed at the National Centre of Infectious and Parasitic Diseases, Sofia, Bulgaria using ELISA and RT-PCR.

ELISA

Serum and CSF samples were tested for WNV-specific IgM and IgG antibodies using ELISA test (Euroimmun, Germany).

RT-PCR

Viral RNAs were extracted from blood and urine samples using QIAmp Viral Mini Kit (Qiagen, Hilde, Germany). WNV RNAs were detected by commercially available real-time RT-PCR kit (Sacace Biotechnologies, Italy).

CASE REPORT 1

A 72-year-old man presented to the hospital with a 6-day history of fever (up to 39°C), fatigue and vomiting. He had been taking NSAID but the treatment had shown no effect. At admission, the patient's body temperature was 37.5°C. The man was oriented to time and place. Neither the physical, nor the neurological examination found any abnormalities. Chest

and cardiac auscultation revealed normal breath sounds and rhythmic heartbeats (88/min, blood pressure 110/70 mmHg, ECG showed normal sinus rhythm without any reporalization and deporalization abnormalities). Nuchal rigidity test as well as Kernig and Brudzinski (upper, middle and lower) signs were negative. Patient's sensitivity was preserved, the cranial nerves were intact and only normal physiological reflexes were found.

No diseases or condition had been documented in the patient's medical history record and he denied taking any medication for a chronic illness.

During the following days, the body temperature returned to normal, but the patient became disoriented to time and place. Furthermore, behavioral changes manifested as periods of aggression, followed by spells of unexpected self-regret and tearfulness. Sleep inversion also presented – the patient slept during the day and stood awake during the night. He was unable to stand on his feet due to severe dizziness. At day 3 after admission, a lumbar puncture was performed. The CSF leaked under normal pressure, it was clear and limpid. Ten days after admission, chest auscultation revealed reduced breath sounds and coarse rales on the left. A chest X-ray confirmed a left-sided pneumonia. At 19 days of hospital stay, abdominal bloating, nausea and inability to produce normal defecation occurred. Physical examination revealed presence of a tender abdominal wall, which deterred deep palpation, a tympanic sound on percussion, and absent peristalsis, the three being clinical features of an acute colonic pseudo-obstruction, known as Ogilvie syndrome. Both complications (the left-sided pneumonia and the Ogilvie syndrome) were successfully treated with medications.

Clinical laboratory findings were within the reference ranges. Microbiological examinations of blood, urine and CSF were negative. Fecal samples were negative for pathogenic bacteria. A laboratory test of CSF showed moderate pleocytosis and proteinorachie ***(Table 1)****.*

The CSF was positive for anti-WNV IgM and HSV-1 DNA (detected by PCR technique).

Serological tests of paired serum samples were performed. The first serum sample (obtained 7 days after onset of disease) was positive for anti-WNV IgM antibodies. Both anti-WNV IgM and anti-WNV IgG antibodies were detected in the second serum sample (obtained 14 days later).

A head CT scan found no vascular changes, hemorrhage or other damage. A T2-weighted head MRI showed a focus of hyperintensity, involving a limited zone of the left temporal lobe, with characteristics similar to those found in HSV-1 encephalitis.

The patient refused consent for a control lumbar puncture to be performed.

The treatment led to a gradual improvement. The patient manifested retrograde amnesia: he could not recall events prior to the occurrence of the abdominal bloating (a manifestation of the acute colonic pseudoobstruction developed).

Upon discharge from hospital 35 days after admission, he showed no mental and behavioral disorders, the neurological and physical examination revealed no abnormalities.

The convalescence was long (it took about a month) with persistent adynamia. An active rehabilitation course under specialist's supervision was implemented. Twenty days after discharge, the patient presented with a partial inability to hear. An audiogram registered a permanent hearing loss of the left ear.

A brain MRI test run 6 months later detected cerebral cortical atrophy and age-associated initial vascular changes. The brain damage in the left temporal lobe was almost repaired.

The following examinations showed the patient was in good health. His relatives found him to be euphoric, unusually talkative and quite physically active.

CASE REPORT 2

A 48-year-old man, who had worked as a builder in Cyprus, presented to the hospital with high fever, fatigue, sleepiness, and dizziness. He had been taking 4 different antibiotics (prescribed to him in Cyprus but he did not have the prescription with him.) since the symptoms had occurred. Nine days after the onset of disease, the patient was admitted to the hospital with high fever (as high as 40°C), bradypsychia and somnolence – the patient fell asleep several times during the examination. His answers were inaccurate and confusing. The physical examination found the presence of right-sided pneumonia – chest auscultation revealed bilateral diminished vesicular breath sounds with crepitations in the right middle and basal lung-field. Neurological examination revealed an ataxic gait, a positive Romberg test and horizontal nystagmus, with both tendon and periosteal hyporeflexia.

After the initiation of therapy, the patient's condition gradually improved. During the following days, body temperature dropped down to normal, and pneumonia completely resolved. Neither qualitative nor quantitative disorders of consciousness were registered.

About a week after admission, the patient developed an acute pancreatitis with typical manifestation: intense abdominal pain, bloated abdomen, nausea and vomiting. The

Table 1. Cerebrospinal fluid: laboratory results

Cell count		Differential leukocyte count		Protein (0.08–0.45) [g/l]	Glucose (2.22–4.44) [mmol/l]	Cl^- (115–132) [mmol/l]	Pandy's reaction
Leuc/mm^3 (0 – 5 mononuclear cells)	Er/mm^3 (0–10)	Sg	Ly				
72	10-12	0.30	0.70	1.12	4.7	131	Pos.

Reference ranges are given in brackets

clinical laboratory tests showed elevation of serum and urine amylase (serum amylase 374 U/l, urine amylase 1297 U/l). Abdominal ultrasonography was performed and only slight dilatation of the pancreatic duct was found.

The results of the clinical laboratory tests of his blood and serum were within the reference ranges. The elevations of serum and urine amylase were relevant to the clinical manifestation of an acute pancreatitis. A CT and MRI scan of the head detected no brain injury.

Diagnosis of WNF was made by serological tests of paired serum samples. The first serum sample (obtained 10 days after onset of disease) was positive for anti-WNV IgM. The second serological test was performed 14 days later and both anti-WNV IgM and anti-WNV IgG antibodies were detected.

Convalescence period was prolonged with persistent dizziness.

CASE REPORT 3

A 56-year-old woman presented to the hospital with fever (up to 39°C), fatigue, sleepiness, dizziness and discoordination. She found difficulties doing ordinary daily activities – she was unable to calculate and answered some questions inaccurately. At that time, she was also experiencing diarrhea. The woman was hospitalized ten days after onset of symptoms. At admission, she was oriented to time and place, but bradypsychic and somnolent. Bradycardia – 47/min and hypotonia 90/60 mmHg were registered. Neurological examination revealed horizontal nystagmus, brisk to clonus tendon and periosteal reflexes, an ataxic gait and a positive Romberg test.

Clinical laboratory tests of her blood and urine were within the reference ranges. The patient's condition gradually improved. The convalescence period was prolonged with persistent dizziness and poor concentration.

The diagnosis was confirmed by detection of WNV-RNA in the blood (10 days after onset of disease). Serological tests detected anti-*WNV IgM in the serum 10 days after onset of disease. The second serological test run 14 days later detected both anti-WNV IgM and anti-WNV IgG antibodies.*

RESULTS

The clinical laboratory results were within the reference ranges in all patients. The elevation of the serum and urine amylase of the second patient was consistent with the acute pancreatitis he developed as a complication.

The laboratory examination of the CSF of the first patient showed moderate pleocytosis and proteinorachie and the microbiological studies of blood, urine, stool and CSF samples were negative for any pathogens.

The MRI scan of the first patient registered changes in the left temporal lobe of the brain, which were typical for HSV-1 encephalitis. The medical imaging of the rest of the patients showed no abnormalities.

According to the criteria of the Commission Implementing Decision (EU) 2018/945 of 22 June 2018, one of the cases presented was classified as probable and two of them were confirmed.

A WNF case is confirmed if it fulfils at least one of the following laboratory criteria: (Commission Implementing Decision (EU) 2018/945 of 22 June 2018 on the communicable diseases and related special health issues to be covered by epidemiological surveillance as well as relevant case definitions).[23]

- Isolation of WNV from blood or CSF;
- Detection of WNV nucleic acid in blood or CSF;
- WNV specific antibody response (IgM) in CSF;
- WNV IgM high titre AND detection of WNV IgG, AND confirmation by neutralisation;

Detection of WNV specific antibody response in serum only, defines a WNF case as probable.[23]

The diagnostic methods and the test results of the patients are presented in **Table 2**.

The first patient was diagnosed with HSV-1 encephalitis

Table 2. Diagnostic methods and test results

Case No	Time of specimen collection	Detection of WNV-specific antibodies in the first serum sample	Detection of WNV-specific antibodies in the second serum sample obtained 14 days later	WNV-RNA in blood detected by PCR	Antibodies detected in CSF	Interpretation
1.	7 days after onset of disease	IgM pos. IgG neg.	IgM pos. IgG pos.	Not detected	IgM pos.	WNND - a confirmed case.
2.	10 days after onset of disease	IgM pos. IgG neg.	IgM pos. IgG pos.	Not detected	Lumbar puncture was not performed	A probable case of WNF
3.	10 days after onset of disease	IgM pos. IgG neg.	IgM pos. IgG pos.	Detected	Lumbar puncture was not performed	A confirmed case of WNF

and WNND. The patient manifested an encephalitic syndrome that included disorientation, psychotic production and behavioural changes, as well as incoordination and ataxia (dizziness and inability to stand on his feet). The CSF samples were positive for anti-WNV IgM, and HSV-1 DNA was also isolated. Both anti-WNV IgM and IgG were detected in the serum.

The second case was classified as probable WNF based on the specific anti-WNV IgM and IgG found in the paired serum samples taken 14 days apart.

In the third patient, a PCR blood test detected WNV-RNA. The diagnosis of WNF was confirmed and supported both anti-WNV IgM and anti-WNV IgG found in the serum.

DISCUSSION

The aim of this study was to focus physicians' attention on the clinical manifestations of the West Nile fever. Over the last few years, the disease has been of frequent occurrence in Bulgaria. A seroprevalence study of the distribution of the WNV infection in Bulgaria showed 1.5% seroprevalence (between May and October 2015, 1451 patients were tested and specific antibodies were detected in 22 of them). The seroprevalence rates were found to be higher in Sofia province and the districts near the Danube river.[24]

In WNF patients, there are no specific clinical laboratory findings in the blood and the serum. Similarly to other types of viral encephalitis, the cerebrospinal fluid in WNND shows mild to moderate pleocytosis (with mononuclear predominance) and elevated protein. In WNV meningitis, in the CSF, atypical-appearing monocytes might be observed. They are similar to those found in benign recurrent meningitis of Mollaret (Mollaret cells).[13]

Imaging studies: the computed tomography (CT) and magnetic resonance imaging (MRI) are unremarkable for establishing an etiological diagnosis. In 50% – 70% of the WNV encephalitis, MRI shows abnormalities that involve the thalamus, basal ganglia and brain stem.[7,13]

The etiological diagnosis of WNF is established by isolation of the virus or presence of viral nucleic acid in the blood, CSF and body fluid samples, and also by detection of specific antibodies in the serum and the CSF (anti-WNV IgM and IgG).

IgM antibodies appear soon after the viremia and may persist for 6 months (or longer). In WNND, anti-WNV IgM are detected in the CSF during the acute phase of infection and sometimes until 40 days (or later) after the onset.[5]

The prognosis of WNF depends on the patients' age, comorbidities, clinical form and course of the disease. The risk factors for a severe clinical course include: 1) age: patients >60 years old; 2) comorbidities: diabetes, chronic kidney disease; 3) immunsuppression.

Myocarditis, pancreatitis and hepatitis are usually observed in severe course WNF.[1,8,9,13,25]

The specimen type and time of collection are of great importance to obtaining proper results. During the first few days of the clinical manifestation of WNF, viral nucleic acid could be found in the blood and the urine. During this period, anti-WNV IgM are likely to be detected in the serum, but their absence does not exclude the diagnosis. A second serum sample obtained ≥14 days later should be tested for antibody detection. Anti-WNV IgM antibodies detection in the CSF confirms the diagnosis – being the largest antibodies, they do not cross the blood-brain barrier i.e. they are synthesised in situ.

The reported patients spent long time outdoors– one of the male patients practiced sports near the riverside every day and usually found mosquito bites at the end of the day; the other one lived in Cyprus for a couple of months working as a builder and was exposed to mosquitoes. The female patient often travelled to Turkey and went for a daily walk outdoors.

The three patients presented with similar symptoms – fever, malaise, dizziness and ataxia (manifested with signs of dizziness, unstable gait, positive Romberg test). Rashes and lymphadenomegaly were found in none of them.

Concerning the first case, we assume there was a co-infection: HSV-1 encephalitis and WNND. The clinical presentation (disorientation, mental and behavioural changes, retrograde amnesia) and the MRI finding (a T2-hyperintense focus in the left temporal lobe of the brain) suggested the predominant significance of HSV-1 neuroinfection which clinical course was aggravated by the WNND. The diagnosis was confirmed by the detection of anti-WNV IgM and HSV-1 DNA in the CSF. Anti-WNV antibodies (both IgM and IgG) were found in paired serum samples, obtained 14 days apart.

Although a thorough literature research has been conducted, no information about the incidence, the clinical course and the probable outcomes of the HSV-1/WNV coinfection has been found.

As for the second patient, the diagnosis of probable WNF was established. The patient developed a clinical manifestation of an acute pancreatitis, confirmed by the laboratory results and sonographic findings. Acute pancreatitis as a complication of WNF has been twice described in the medical literature – in an 80-year-old man with WNV – meningoencephalitis and myocardial infarction, and in a 20-year-old woman diagnosed with WNF confirmed by antibody detection in the serum and the CSF.[26]

All patients presented were treated with symptomatic and pathogenetic agents that included glucose and saline solutions, antiedematous agents – Mannitol (administered for 5 days to all patients) and furosemide (administered occasionally) in adequate doses, as well as vitamins (B1, B2, B3, B6, B9, B12), antipyretics (paracetamol, metamyzole), nootropic medications (pyracetam) and a short course of dexamethasone with dose reduction (the course duration depended on the patient's condition). Antibiotics – III generation cephalosporins (Cefoperazon) in therapeutic doses (2g/24h given twice a day until the pneumonia resolved), were administered to both male patients due to the pneumonia.

In view of the HSV-1/WNV coinfection, the first patient was also treated with intravenous Acyclovir. The therapy was started right after the lumbar puncture had been performed. Acyclovir was administered in a daily dose of 2g/24h, given in 4 divided doses for 21 days. The treatment along with the diuretics, dexamethasone (administered for 8 days), symptomatic and pathogenetic agents led to the gradual improvement of the patient mental and behavioural status. The diagnosis of HSV-1 encephalitis was supported by the positive PCR CSF test for HSV-1 DNA and the head MRI. In addition, the treatment with Acyclovir showed to be effective in the management of the encephalitic syndrome.

The anti-WNV IgM antibodies found in the CSF sample confirmed the diagnosis of WNND. The course of HSV-1 encephalitis was aggravated by the WNND. The HSV-1/WNV coinfection led to a prolonged illness with the development of serious complications such as pneumonia and Ogilvie syndrome and a permanent hearing loss. The patient spent 35 days in hospital and continued with rehabilitation at home.

The complications observed in the first and the second patients were Ogilvie syndrome and acute pancreatitis. They were successfully treated with dietary changes and medications – anticholinergics (papaverin, drotaverine, scopolamine), prokinetics (metoclopramide), laxatives (bisacodyle), enzymes secretion inhibitors (somatostatine), KCl and analgesics (metamizole, tramadole).

The course of the disease in all of the patients was acute and resulted in full recovery in two of them. The first patient, coinfected with HSV-1/WNV developed a permanent unilateral hearing loss.

The three of them had a prolonged convalescent period with persistent weakness, fatigue and dizziness.

CONCLUSIONS

The patients described in this paper had symptoms and signs of WNV infection. This article demonstrates a rare case of HSV-1/WNV coinfection manifested with signs of both HSV-1 encephalitis and WNND and confirmed by tests of serum and CSF samples. This patient developed Ogilvie syndrome and hearing loss of the left ear as permanent complications. Another unusual complication of WNF was also observed – the second patient developed an acute pancreatitis, diagnosed by laboratory and sonographic examination.

Although there are no symptoms, signs, laboratory or imaging findings specific for the WNV infection, its clinical course and the possible complication could be life-threatening. Therefore, it is advisable to take WNF into account during summer time (August and September) especially in patients who present with neurological manifestations, travel to endemic regions, spend a long time outdoors and are exposed to mosquito bites.

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Лихорадка Западного Нила – клинические и эпидемиологические характеристики. Обзор литературы и вклад в три клинических случая

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Резюме

Лихорадка Западного Нила (ЛЗН) – это трансмиссивная инфекция, вызываемая *Flavivirus*-вирусом лихорадки Западного Нила (ВЗН). ВЗН передаётся комарами, а птицы являются основным естественным резервуаром. В последнее время зарегистрировано увеличение числа случаев ЛЗН в Европе, на Балканах и в Болгарии. Здесь представлены клиническое течение, лабораторные данные и рентгенологические данные трёх пациентов – одной женщины и двух мужчин, которым был поставлен диагноз ЛЗН. Их изучали в рамках эпидемиологического исследования и с помощью клинического наблюдения, лабораторных и микробиологических методов, серологических тестов на специфические антитела против ВЗН, молекулярных и биологических методов (полимеразная цепная реакция, PCR), компьютерной томографии (КТ) и магнитно-резонансной томографии (МРТ). У пациентов с жаром, сонливостью и головокружением были обнаружены антитела против ВЗН в их сыворотках. ВЗН-РНК была обнаружена в образце крови пациента. Как анти-ВЗН IgM, так и ДНК Herpes simplex virus-1 были обнаружены в образце спинномозговой жидкости одного из мужчин. Трое пациентов выздоровели после длительного периода выздоровления. ЛЗН не имеет специфических признаков, лабораторных и визуальных данных и может быть опасным для жизни состоянием, приводящим к серьёзным осложнениям. Поэтому следует учитывать опасность проявления ЛЗН летом, когда переносчик инфекции активен.

Ключевые слова

атаксия, головокружение, головная боль, лихорадка, вирус лихорадки Западного Нила