West Nile virus meningitis presenting with migrainous headache

Migrenöz baş ağrısıyla prezente olan batı Nil virüsü menenjiti

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Summary
West Nile Virus (WNV) infection is a clinical picture that is transmitted from wild birds, its natural host, to humans through mosquitoes and generally shows an asymptomatic course. Influenza-like WNV fever is frequently seen in symptomatic individuals, and a neuroinvasive course is more rarely observed. Neuroinvasive WNV has a broad-spectrum profile of neurological signs and symptoms. WNV meningitis is one of the most common neuroinvasive forms of WNV, and it does not differ clinically and radiologically from other viral meningitis. Secondary headaches, which can mimic primary headaches, are an infectious factor that should be kept in mind in the etiology, especially in cases presenting in the summer months. In this study, a case of WNV meningitis presenting with a headache of migrainous character is presented.

Keywords: Headache; migraine; west Nile virus.

Introduction
West Nile virus (WNV) is a positive polarity, single-stranded RNA virus belonging to the genus Flavivirus of the Flaviviridae family.1 Arthropod (ticks and mosquitoes) mediated transmission causes disease, especially in horses and humans.2 The most common route of transmission in humans is mosquito bite, followed by blood transfusion,3 organ transplantation,4 transplacental transmission,5 breast milk transmission,6 and occupational exposure in laboratory workers.7 Acute signs of infection may occur in 20–40% of infected individuals 2–14 days after virus transmission.8 The clinical manifestations of the disease are like those of classical influenza infection, including fever, headache, myalgia, anorexia, nausea and vomiting, and abdominal pain.9,10

The neuroinvasive form, which is the rarest involvement pattern and is encountered in approximately 1–5% of all WNV infections, occurs by direct viral invasion of endothelial cells in the cerebral microcirculation or by the virus reaching the central nervous system via the olfactory bulb via the trans neuronal route.11 Neuroinvasive disease can lead to clinical conditions such as meningitis, encephalitis, and acute flaccid paralysis, confusion, and coma accompanied by systemic fever, which can cause serious morbidity and mortality.12 It has been reported in the literature that encephalitis is more common in the older age group, while meningitis is more common in the child and young adult age group.13,14 Less common clinical presentations during neuroinvasive disease are brainstem encephalitis, cerebellitis, cerebral palsy, polynuropathies, polyneuropathy/radiculopathy,
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In this study, a case of WNV meningitis is presented, the first symptom of which was a typical migrainous headache and in which central nervous system infection was suspected and diagnosed during the disease.

**Case Report**

A 24-year-old female patient without any chronic disease presented to the emergency department with a headache. The patient described a bifrontal and throbbing pain that had been ongoing for two days, accompanied by phonophobia, photophobia, osmophobia, and nausea and vomiting. The headache, which could reach a severity of 10/10 intermittently but was generally 5–6/10, was partially responsive to nonsteroidal anti-inflammatory treatment. It did not exhibit positional characteristics and was not accompanied by autonomic findings. It was learned that the patient had been evaluated for similar headache attacks one month before her emergency presentation and was started on duloxetine with a preliminary diagnosis of tension-type headache. The patient had a history of oral contraceptive use and smoking.

The patient, whose neurological examination was normal and in whom no acute pathology was detected in the non-contrast cranial CT examination, was initially considered to have a migraine headache attack without aura and was followed up with symptomatic treatment. During the follow-up period, the patient’s cranial imaging was updated in detail due to the worsening of the headaches, the addition of positional character, and the emergence of meningeal irritation findings in the repeated neurological examination. Non-contrast cranial CT, diffusion MR, contrast cranial MR, and MR venography examinations were within normal limits. Lumbar puncture was performed on the patient with the preliminary diagnoses of subarachnoid hemorrhage and venous sinus thrombosis. CSF opening pressure was 36 cm H$_2$O, CSF protein was 110 mg/dl, and CSF glucose was measured within normal limits. In the CSF, while no erythrocytes were observed, 320/mm$^3$ leukocytes were seen with lymphocyte dominance. Although her vital signs were stable and fever-free, the patient was diagnosed with meningitis and started on empirical vancomycin and ceftriaxone treatment with clinical and CSF findings. Routine hemogram, liver and kidney function tests, and electrolyte levels were within normal limits. Hepatitis and HIV serology, aerobic and anaerobic bacterial cultures, viral meningitis panel (adenovirus, EBV, CMV, HSV-1, HSV-2, VZV, HHV-6, HHV-7, enterovirus, parvovirus B19), TBC PCR, and TBC culture were negative.

The patient’s clinical findings regressed in the first days under empirical antibiotic therapy, and the second clinical worsening episode occurred on the 10th day after the end of the treatments. No pathology was observed in the renewed cranial imaging of the patient, whose headache complaints recurred and who had widespread myalgia complaints. A second lumbar puncture was performed for the differential diagnosis of infectious etiologies. CSF opening pressure was 20 cm H$_2$O, CSF protein was 73 mg/dl, and CSF glucose was measured within normal limits. CSF sample showed 30/mm$^3$ leukocytes with a neutrophil predominance. Routine CSF microbiology panels were negative for viral, bacterial, and fungal infections. Since the patient’s anamnesis included a travel history to the Aegean Region 15 days ago and intense mosquito exposure, it was planned to investigate for possible West Nile virus infection. Serum samples were sent to the T.R. Ministry of Health, General Directorate of Public Health, National Arbovirus and Viral Zoonotic Diseases Laboratory for BNV serology and molecular (polymerase chain reaction-PCR) screening tests. In the serum sample, BNV IgM and IgG antibodies (IFA method) were positive, and BNV PCR was negative. In the tests repeated eight days later, it was seen that IgM antibodies became negative and IgG antibody positivity continued. It was planned to study BNV serology in the CSF sample for laboratory confirmation of neuroinvasion, but since the patient refused lumbar puncture, BNV IgM could not be studied in the CSF sample. The patient, who was evaluated as having BNV meningitis with the serum BNV serology results, was given symptomatic pain palliation and hydration treatment. Complete regression was observed in the patient’s current symptoms within a period of one month. No clinical relapse was detected in the two-year follow-up.
Discussion

In our country, WNV was first detected in August 2010 in cases that applied to Manisa State Hospital with high fever and confusion. WNV infection causes small epidemics every summer and can cause variable, severe, and fatal clinical findings with its neuroinvasive form seen in 1–5% of cases. The first WNV meningoencephalitis case from Istanbul was reported in 2017, and 7 cases were reported from Istanbul until August 2019, when the case we presented applied to our hospital. Our case was presented because the patient applied to the neurology clinic with a migraine headache and reminded us of the importance of WNV as a seasonal viral meningitis-encephalitis agent in addition to routine infectious agents among secondary headache causes.

WNV meningitis is characterized by fever, headache, meningeal irritation findings, and photophobia, as in other viral meningitis. Headache alone is not a distinguishing feature and may resemble all secondary headaches. Acute/subacute onset and accompanying systemic infection findings are warning signs and should be evaluated as red flags of headache. Nonspecific cranial MRI findings that may be detected during WNV meningitis vary according to the level of meningeal involvement and parenchymal involvement and are no different from other infectious meningitis involvements. In West Nile virus central nervous system involvement, increased protein titer (<150 mg/dl) in CSF, moderate pleocytosis (<500 cells/mm³) with lymphocyte dominance, and plasmacytoid lymphocytes or large monocytic cells can be detected in cytological examination.

The basis of the diagnostic workup is the detection of WNV IgM antibodies in serum or CSF. A positive WNV IgM result is often sufficient for diagnosis. Neutralization tests are performed in the presence of suspicion of cross-reactivity with other flavivirus infection agents. If the initial antibody test is negative but clinical suspicion persists, it is recommended to repeat the antibody test after 10 days. WNV IgG antibodies have no role in the diagnosis of acute WNV infection. Seroconversion from WNV IgM antibodies to WNV IgG antibodies occurs between days 4 and 10 of viremia. Demonstration of antibody presence in CSF is necessary to confirm the presence of neuroinvasive disease.

WNV meningitis is often a self-limiting clinical condition and has no specific treatment. Symptomatic pain palliation and hydration practices and close clinical follow-up are recommended to prevent secondary bacterial infections and complications related to hospitalization/mobilization restriction. It has been reported that fatigue, forgetfulness, balance problems, and headache complaints may persist for many years in patients after the acute infection period. There is no licensed vaccine formulation that can be applied to humans for protection against WNV infection.

In conclusion, WNV meningitis, like all other secondary headache etiologies, can mimic primary headache forms and cause diagnostic difficulties. In cases presenting with acute-subacute onset headache, especially in the summer season, a history of mosquito contact should be questioned in the presence of concomitant systemic infection findings. It is a clinical entity that should be kept in mind in endemic regions and certain seasons, and reference laboratories should be contacted, and diagnosis should be made with serological and molecular examination of serum and CSF samples.

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