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Case Report

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High cerebrospinal fluid protein level in West Nile virus encephalitis: report of five cases*

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Abstract: An outbreak of West Nile virus (WNV) occurred in Greece, Russia, and Turkey in 2010. We diagnosed 5 WNV encephalitis patients, who presented with high cerebrospinal fluid (CSF) protein level and encephalitis relevant symptoms in the last days of summer or in the first days of autumn. Here, we aimed to present a retrospective analysis of 5 WNV encephalitis cases in Turkey in terms of their clinical and laboratory findings.

Key words: West Nile virus, encephalitis, cerebrospinal fluid protein

Introduction

West Nile virus (WNV) is a member of the family Flaviviridae, which also includes the viruses causing yellow fever, dengue fever, and tick-borne encephalitis. WNV has been responsible for morbidity and mortality of thousands of cases in animals and humans. WNV has been detected in different parts of the world such as the Middle East, Europe, and Africa. It mainly causes a mild-moderate febrile illness in human. The clinical presentation of the disease varies from asymptomatic (nearly 80% of infections) to encephalitis/paralysis and death (<1% of infections). There is no antiviral therapy or licensed vaccine for humans (1,2).

In recent years, especially in the USA, Asia, Africa, the Middle East, the Balkans, and in Eastern and Southern Europe, WNV infection has been responsible for the deaths of a number of people, horses, and birds. WNV was first recognized in Turkey in the 1960s by seroprevalence studies. In August 2010, a number of encephalitis cases broke out in Manisa Province. A total of 47 cases of WNV were confirmed in Turkey at this time, and 8 cases resulted in death (unpublished data from Dr. Handan Kalaycıoğlu, Ankara, Turkey). The other cases were reported from different parts of Turkey. Meanwhile, other cases were reported in Greece and Russia as well (3). WNV is expected to be highly active next spring and summer and may be a serious problem in Turkey. In this report, we aimed to share our clinical and laboratory findings from patients acutely infected with WNV in the spring of 2010.

Cases

All patients presented with fever and general deterioration, while only 4 patients (80%) presented with headache and confusion. Patients considered to be suffering from encephalitis had fever and general deterioration. History of mosquito bite and diabetes mellitus was reported in 3 patients (60%). Skin eruption, lymphadenopathy, and stinging sensation in the eyes were not reported and only 1 patient had nausea, vomiting, and diarrhea. None of the patients died. The mean lymphocyte count of

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CSF was 220 mm^3 and the mean protein level of CSF was 546 mg/dL. Laboratory findings of the patients are summarized in Table 1.

Case 1

A 65-year-old man presented to our clinic with confusion, vomiting, headache, fever, and nausea. Hypertension (for 10 years) and diabetes mellitus (for 5 years) were reported in his medical history. Neck stiffness and meningeal irritation findings (MIF) were not observed. He had pancytopenia and also 50/mm^3 cells (lymphocyte predominance) and 687 mg/dL protein level were observed in the CSF examination. Other CSF findings are summarized in Table 2. There was no pathological finding in brain computed tomography. Viral encephalitis and acute meningitis were determined in the differential diagnosis. The patient was treated with ceftriaxone 2 × 2 g/day and acyclovir 3 × 750 mg/day. He recovered during the 14-day follow-up.

Case 2

A 78-year-old man presented to our clinic with fever, headache, and confusion. Neck stiffness and MIF were absent. Lumbar puncture (LP) was done and CSF examination of the patient revealed 80/mm^3 cells (lymphocyte predominance) and 666 mg/dL protein level. Chronic lacunar infarct was seen in the brain CT. Viral meningoencephalitis was determined in the differential diagnosis. The patient was treated with ceftriaxone 2 × 2 g/day and acyclovir 3 × 750 mg/day. He completely recovered and was discharged on day 14 of follow-up.

Case 3

A 34-year-old man was admitted to our clinic with fever and headache. Neck stiffness was observed. A total of 570/mm^3 cells (lymphocyte predominance) was seen in the CFS examination. There was no pathological finding in the brain CT. Acute bacterial

Table 1. Demographic and clinical findings from patients with WNV infection.

PARAMETER	Case 1	Case 2	Case 3	Case 4	Case 5	Avg.	(Min-Max)
Age	65	78	34	82	72	66.2	34-82
Sex	M	M	M	M	M		
Rural/Urban	U	R	U	U	U		
WBC K/µL	2.9	12.9	11.4	8.1	11.3	9	2.9-12.9
Hgb g/dL	12.9	15.4	14.6	14	12.6	14	12.6-15.4
Plt K/µL	58	242	132	241	145	164	58-242
CRP mg/L	6	24.3	37.9	13.6	84.2	33	6-84.2
ESR mm/h *	9	47	21	33	57	33	9-57
Glucose mg/dL	137	95	84	236	121	135	84-236
AST IU/L	28	27	38	15	29	27	15-38
ALT IU/L	22	11	27	11	28	20	11-28
CK IU/L	NA	2341	231	NA	124	899	124-2341

NA: No Data Available. ESR = Erythrocyte sedimentation rate

Table 2. CSF findings from patients with WNV infection.

CSF findings	Case 1	Case 2	Case 3	Case 4	Case 5	Avg
Cell count	50	80	570	NA	180	220
Cell predominance	Lymphocyte	Lymphocyte	Lymphocyte	NA	Lymphocyte	
Protein (mg/dL)	687	666	681	NA	148	546
Glucose	87	45	59	NA	113	76
Na (mmol/L)	147.6	149	140	NA	142	145
Cl (mmol/L)	112	120	114	NA	122	117

NA: No data available

meningitis was diagnosed and the patient was treated with ceftriaxone 2 × 2 g/day and vancomycin 4 × 0.5 g/day. Acyclovir was added to the therapy due to persistent symptoms after day 3 of treatment. A second LP was done and his cell count was 150/mm^3 on day 5 of treatment. His symptoms had resolved by day 14 of follow-up and he was discharged.

Case 4

An 82-year-old man was admitted to our clinic with fever and headache. No neck stiffness was observed in his physical examination. He had a 10-year history of hypertension and diabetes mellitus. Encephalitis was determined but LP could not be implemented as the patient did not agree to it. He discharged himself on the second day after admission.

Case 5

A 72-year-old man presented with fever, confusion, and headache. He had a 10-year history of diabetes mellitus. Neck stiffness was observed but other MIF signs were absent. The CSF examination of the patient revealed 180/mm^3 cells (lymphocyte predominance). There was no pathological finding in the cranium CT. The patient was treated with ampicillin/sulbactam 4 × 1 g/day, acyclovir 3 × 750 mg/day, and moxifloxacin 400 mg/day. He was discharged fully recovered after 14 days of treatment.

Discussion

WNV can cause epidemics in the summer and the first days of autumn through mosquito bites. The disease was reported in America, Africa, Middle East, and temperate regions of Europe. Many epidemics were reported in Israel, South Africa, Algeria, Tunisia, France, America, Greece, and Russia (4). There are 2 reasons for the timing of such epidemics. First, during this time of the year, the temperature rises and becomes ideal for breeding mosquitoes. Second, the immigration of birds occurs during this period, and birds can spread the disease from district to district and from country to country (5,6). We identified that patients' admission times were similar. WNV must be taken into account in patients admitted with encephalitis at the end of summer, and so they should be examined with serological and molecular tests for diagnosis.

The progress of WNV infection is mostly mild or asymptomatic. Headache, fever, myalgia, skin eruptions, and lymphadenopathy are observed in symptomatic WNV infections. Encephalitis, fever, numbness, cognitive dysfunction, confusion, coma, muscle spasms, and paralysis can be seen in severe cases. Mortality rate was reported as 3%-15% but it could be higher in the elderly (3). All patients but one were older than 60 years in our study as well. We consider that the virus progresses asymptomatically in younger persons but results in encephalitis in elderly patients. In Turkey, physicians should be

aware that if patient is older than 60 years old and presents with high fever, headache, and general deterioration during summer or autumn and comes from the temperate regions of the country, WNV could be a possible diagnosis.

The most common symptoms of the 5 patients with WVN infection in our study were fever, general deterioration, and confusion. These symptoms are frequently observed in WNV infection (7-9). However, in contrast to other reports, none of our patients had any skin eruptions, lymphadenopathy, or stinging of the eyes. This could be related to the differentiation of the virus over the years, geographical differences, and the small number of cases in our study. The progression of WNV infection is more severe in the elderly due to their weakened immune systems (10).

WNV causes aseptic meningitis with slight increases in the CSF cells and protein as observed in patients with aseptic meningitis (11). In many cases of viral encephalitis, the mean protein level is 150 mg/dL (12). However, among our cases, the mean protein level was higher compared to other cases of viral encephalitis and aseptic meningitis. This finding has also been reported previously. Petzold et al. (13) revealed that aseptic meningitis was diagnosed in 7 of 24 patients with WNV infection and the higher protein level could be related to neuron death and glial disorders in BNV encephalitis.

WNV could cause multifactorial disorders in the blood-brain barrier by affecting molecular factors in the brain. Wang et al. (14) proved that the virus caused tense spots in the blood-brain barrier by catalyzing matrix metalloproteinase (MMP). Catalysis of MMP proteins increases white blood cell migration into the CSF and the protein level of CSF. Expansion of a tight junction affects the basal membrane structure and impaired regions may result in increased CSF protein. Although the pathogenesis has not been explained yet, increased permeability in the endothelial cells has been thought to be responsible due to numerous cytokines. The WNV infects the brain, cerebral peduncle, and neurons of the spinal cord; it damages particularly the cerebral trunk and the spinal cord anterior horn cells. The other neurons around the infected neurons are also affected by the damage caused by the virus. The virus itself also causes nerve damage. With articles and findings relevant to our study, if a patient has encephalitis relevant symptoms and higher CSF protein level, WNV encephalitis should be considered as a possible diagnosis (15,16).

In conclusion, our analysis of 5 serial patients with WNV encephalitis revealed that infection is seen particularly in the elderly and the protein level of CSF is higher compared to other viral encephalitis cases. If CSF protein level is high in a patient presenting with encephalitis symptoms at the end of summer or the beginning of autumn, that patient should be tested for WNV infection.

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