



# WEST NILE VIRUS INFECTION WITH NEUROLOGICAL DISORDERS: A CASE REPORT AND A BRIEF REVIEW OF THE SITUATION IN BULGARIA

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**SUMMARY** – A case of a 66-year-old man with West Nile neuroinvasive disease manifested with fever, weakness, fatigue, consciousness disorders and underlying diabetes mellitus type 2 and cardiovascular diseases is presented. Laboratory data showed elevated erythrocyte sedimentation rate and fibrinogen. Serological tests revealed West Nile virus specific antibodies of class IgM and IgG in serum. West Nile virus RNA was detected in urine sample. Supportive therapy was applied.

**Key words:** *West Nile virus; West Nile fever; Antibodies; RNA, Viral; Nervous system diseases; Case reports; Bulgaria*

## Introduction

West Nile virus (WNV), a single-stranded RNA virus, is a mosquito-borne flavivirus (family *Flaviviridae*)<sup>1</sup>. The natural cycle is realized by transmission between mosquitoes of *Culex* spp. and several bird species<sup>2</sup>. Horses and humans are incidental dead-end hosts<sup>3</sup>. Generally, human infections are asymptomatic, acute febrile syndrome is presented in 10%-20% of cases, and less than 1% of them developed neuroinvasive disease<sup>3</sup>. The first large outbreak in Europe was in Romania in 1996<sup>4</sup>. Since then, sporadic cases were reported until another outbreak occurred in Greece in 2010<sup>5</sup>. Reports followed on human outbreaks or sporadic cases in countries from south-east Europe (Bulgaria, Croatia, Greece, Romania, Serbia, Turkey)<sup>6-13</sup>.

A case report of laboratory confirmed human case of WNV infection with neurological symptoms and favorable outcome is presented.

## Case Report

A 66-year-old man presented to the Emergency Center, Military Medical Academy, Sofia, Bulgaria, on September 7, 2016, because of low-grade fever, palpitation, fatigue, extremity weakness, dizziness, headache, and brief loss of consciousness three days before hospital admission. The man had concomitant diabetes mellitus type 2, hypertension, paroxysmal atrial fibrillation, mitral valve regurgitation and tricuspid valve regurgitation. The patient was a retiree and lived in Sofia. He did outdoor activities such as fishing and hiking and mentioned mosquito bites during the summer of 2016. Upon admission, he was afebrile, conscious, with blood pressure 150/80 mm Hg, heart rate 90/min; the rest of physical examination did not show any abnormalities. Neurological examination did not estimate neck stiffness or symptoms of Kernig and Brudzinski at the time of hospitalization. The main laboratory findings were as follows: white blood cell count  $7.3 \times 10^9/L$  (reference range:  $3.5-10.5 \times 10^9/L$ ), platelets  $144 \times 10^9/L$  ( $150-400 \times 10^9/L$ ), hemoglobin 146 g/L ( $130-180 \text{g/L}$ ), erythrocyte sedimentation rate 50 mm/h ( $\leq 20$  mm/h), blood glucose 9.4 mmol/L ( $3.5-5.6$

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mmol/L), creatinine 112  $\mu\text{mol/L}$  (45-130  $\mu\text{mol/L}$ ), urea 4.7 mmol/L (2.8-8.3 mmol/L), aspartate aminotransferase 40 IU/L (5-40 IU/L), alanine aminotransferase 27 IU/L (5-40 IU/L), creatine phosphokinase 193 IU/L ( $\leq 180$  IU/L), C-reactive protein 3.6 mg/L (0.0-5.0 mg/L), potassium 4.2 mmol/L (3.5-5.2 mmol/L), sodium 137 mmol/L (136-145 mmol/L), and fibrinogen 5.21 g/L (2.0-4.5 g/L). Imaging investigations were done at the beginning of illness. Electrocardiogram, x-ray and abdominal ultrasound did not show any abnormalities. Transthoracic echocardiogram revealed the underlying cardiac pathology. Empirical antimicrobial drug therapy was started (intravenous cefoperazone/sulbactam 1 g twice daily and amikacin 500 mg twice daily). The patient received supportive treatment as well. In a short period of hospitalization, consciousness disorders developed and WNV infection was suspected. The man was transferred to Department of Infectious Diseases. He became aggressive and excitable with a tendency of drowsiness. Neurological examination found right facial palsy and areflexia of lower extremities. No lumbar puncture was performed as the patient refused the invasive procedure. Computed tomography of the head was normal. Serum samples were obtained for serological tests for WNV, TBEV, influenza A virus, influenza B virus and *Borrelia burgdorferi*. All results were negative except for the positive result for specific IgM antibodies against WNV in serum sample. On day 7 of the illness, second blood and urine samples were obtained and transferred to the National Reference Laboratory of Vector-Borne Infections, Department of Microbiology, National Center of Infectious and Parasitic Diseases, Sofia, Bulgaria. Specific WNV-IgM antibodies were detected in serum (Anti-WNV ELISA IgM, Euroimmun, Lübeck, Germany), but specific WNV-IgG antibodies were not found (Anti-WNV ELISA IgG, Euroimmun, Lübeck, Germany). Blood and urine samples were tested for WNV RNA using a commercial kit (Sacace Biotechnologies, Como, Italy). The results were negative. One week later, blood and urine samples were obtained for confirmation. The level of IgM antibodies was elevated and specific IgG antibodies against WNV were detected. WNV RNA was detected in urine sample by real-time polymerase chain reaction (PCR). Blood cultures showed no bacterial growth. Neurological manifestations were re-

versible and in a few days the patient regained normal consciousness. After complex therapy, the patient was discharged. On three-month follow-up, the patient was free from any neurological complications.

## Discussion

Bulgaria is situated in the south-east part of Europe, with Mediterranean climate, a field for migratory and overwintering birds. During the last decades, the neighboring countries reported human WNV outbreaks and sporadic cases in new areas<sup>10-17</sup>.

In the 2011-2016 period, the Bulgarian Reference Laboratory of Vector-Borne Infections (Sofia, Bulgaria) reported only nine human cases, of which six cases fulfilled the EU criteria for probable WNV cases and three cases were laboratory confirmed<sup>6-8,18</sup>. During these six years, only three confirmed human cases at the time of increasing emergence of WNV in Europe were recorded. It is logically to expect more human cases in Bulgaria because of the favorable geographic location, suitable climate factors, vectors, and an increasing incidence of cases along the Danube River and in northern Greece.

The seroprevalence of WNV among healthy people in Bulgaria in 11 provinces of the country showed the highest WNV seropositivity in the Sofia district<sup>19</sup>. Hadjichristodoulou *et al.* report 2.1% WNV seropositivity in Greece<sup>20</sup>. Kalaycioglu *et al.* and Gazi *et al.* identified seroprevalence of WNV in Turkey of 3.8% and 4.3%, respectively<sup>21,22</sup>. Obviously, the levels of WNV seropositivity are similar across south-east Europe.

The surveillance systems, veterinary control, medical attention to this infection and collaboration among different institutions in Bulgaria are unsatisfactory. Medical doctors should actively search for WNV infection and epidemiological data on mosquito bites in case of acute febrile syndrome with/without neurological signs in summer/autumn season (July-October).

The clinical case of WNV infection presented was an elderly man with concomitant diseases. Male gender is reported as predominant in Serbian and Romanian reports of WNV cases<sup>11,12</sup>. Mean age of more than 65 years and diabetes are significantly associated with encephalitis, as reported by Popovic *et al.*<sup>12</sup>. Hypertension is one of the main underlying conditions estimated in European outbreaks<sup>9,11,12</sup>. Notably, these concomitant diseases increased the chance for WNV

manifestation with neuroinvasive disease in patients presenting neurological signs, while involvement of the nervous system in the development of WNV infection has been recognized as a tendency in the last decade in Europe, mainly associated with establishment of WNV lineage 2 in the continent<sup>14,23</sup>.

In conclusion, a case report of a 66-year-old man with underlying diabetes mellitus type 2 and cardiovascular diseases, who developed consciousness disturbances and neurological signs as a result of neuroinvasive infection with WNV is presented. The etiological agent was laboratory confirmed based on the EU recommendation<sup>18</sup>. Specific antibodies of IgM and IgG classes against WNV were found in serum samples. WNV RNA was detected by real-time PCR in urine sample<sup>24</sup>. Complex clinical symptoms, physical findings and laboratory investigations confirmed the clinical case of WNV infection in an elderly man with neurological signs, who recovered without consequences.

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#### Sažetak

### INFEKCIJA VIRUSOM ZAPADNOG NILA S NEUROLOŠKIM POREMEĆAJIMA: PRIKAZ SLUČAJA I KRATAK PREGLED STANJA U BUGARSKOJ

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Prikazuje se slučaj 66-godišnjeg bolesnika s neuroin vazivnom bolešću Zapadnog Nila koja se manifestirala groznicom, umorom, poremećajem svijesti uz osnovnu bolest dijabetesa tipa 2 i kardiovaskularnom bolešću. Laboratorijski podaci pokazali su povišenu sedimentaciju i fibrinogen. Serološki testovi utvrdili su protutijela specifična za virus Zapadnog Nila klase IgM i IgG u serumu. Virusna RNA otkrivena je u uzorku mokraće. Primijenjena je suportivna terapija.

Ključne riječi: *Virus Zapadnog Nila; Groznica Zapadnog Nila; Antitijela; RNA, virusna; Neurološke bolesti; Prikazi slučaja; Bugarska*