Non-neuroinvasive West Nile virus infections during the outbreak in Greece

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Abstract

A major outbreak of West Nile virus (WNV) infections took place in 2010 in Greece. Apart from the neuroinvasive cases, many additional cases without involvement of the nervous system were observed, characterized by high fever, myalgia, rash, leukopenia, and long-lasting recovery. West Nile non-neuroinvasive disease is a distinct clinical syndrome, and is not always mild.

Keywords: Greece, leukopenia, non-neuroinvasive disease, outbreak, West Nile virus

Original Submission: 6 July 2011; **Accepted:** 25 July 2011
Editor: R. Charrel
Article published online: 27 July 2011
Clin Microbiol Infect 2011; **17:** 1681–1683
10.1111/j.1469-0691.2011.03642.x

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West Nile virus (WNV) infections are usually asymptomatic or mild, and are referred to as West Nile fever [1,2]. Approximately 20% of the infections present with fever, often accompanied by rash, and <1% present as neuroinvasive disease (West Nile neuroinvasive disease (WNND)) (mainly encephalitis or meningoencephalitis). Although recovery from mild infections is complete, involvement of the central nervous system is associated with a mortality rate of up to 10% and long-term morbidity [3]. CCR5 deficiency increases the risk of symptomatic infection, and depressed immunity, age and underlying diseases are correlated with greater risk of WNND [4].

During July to October 2010, a large-scale WNV outbreak occurred in Greece [5]. Over a 14-week period, 197 WNND cases were reported [6]. Lineage 2 WNV was detected in individual donation-nucleic acid testing-positive blood donors, and in mosquitoes [7,8] (A. Papa, C. Politis, A. Tsoukala, A. Eglezou, V. Bakaloudi, M. Hatzitaki, K. Tsergouli, submitted). The highest WNND incidence was seen in Pella and Imathia prefectures in Central Macedonia, northern Greece (28.26 and 27.06 per 100 000 population, respectively).

Apart from the WNND cases, 65 West Nile non-neuroinvasive disease (WNNND) cases were reported. This represents only a partial number, as the number of patients presenting to the hospitals and health centres in the affected areas, with fever, headache, myalgia, arthralgia, and rash, was extremely high. The aim of the present study was to describe the clinical manifestations of the WNNND cases during the outbreak of WNV infections in 2010 in Greece.

The study took place in Giannitsa, the largest city of Pella prefecture (the one with the highest incidence). During July to October 2010, 29 patients (15 male) with encephalitis or encephalomyelitis were hospitalized in Giannitsa General Hospital. Their median age was 74 years (range, 25–87 years). Ten patients died. During the same period, an unexpectedly high number of younger patients presented to the hospital with sudden onset of fever, frontal and occipital headache, severe dizziness, gait instability, malaise, myalgia, muscular weakness, back pain, and arthralgia. Many patients presented nausea, vomiting, anorexia, and diarrhoea, and 60–70% presented roseoral or maculopapular rash without pruritus, which occurred in the middle or late course of the disease, mainly on the trunk, neck, and upper limbs, lasted for about 4–5 days, and disappeared with the decline of fever. The fever was as high as 40°C, and lasted for a few days to 2–3 weeks. The persistence of high fever, the intense malaise and anorexia led to a large number of patients experiencing weight loss of up to 10–15 kg. The main laboratory finding was leukopenia, lasting for 6–10 days, and the initial finding was mononucleosis, which decreased with the onset of leukopenia. Convalescence lasted for several days, or even months, and during this time patients experienced severe fatigue and malaise.

Serum samples of the first patients drawn on the first visit to the hospital were negative for WNV antibodies, which were detectable in the follow-up samples; it was soon realized that antibodies present later in WNNND than in

WNND [9]. It was estimated that, during the 4-month period, 300 patients with suspected WNNND visited the hospital. Four were hospitalized. Symptomatic treatment was administered, and psychological support was often needed, because of the fear of imminent death.

In order to determine whether WNV was the cause of the disease, patients were informed about the study and agreed to be tested for the presence of WNV IgM and IgG antibodies. One hundred patients responded to the call (response rate, 33.3%); a sample was obtained 2–4 months after onset of the illness. Detection of WNV IgM and IgG antibodies was achieved with ELISA (WNV IgM capture DxSelect and WNV IgG DxSelect; Focus Diagnostics, Cypress, CA, USA).

Ninety-five (95%) patients were WNV antibody-positive: 82 for both IgM and IgG, and seven for IgG, with IgM titres close to the cut-off value (these patients were tested 4 months after onset of the illness). Among the 95 patients, 35 (36.84%) were male and 60 (63.16%) were female, aged 16–80 years (mean, 51.7 years; standard deviation (SD), 17.1). The main clinical signs and symptoms are shown in Table 1. Fever (mean, 38.5°C; SD, 0.77), fatigue, headache and arthralgia/myalgia were the most common symptoms. Sixty-one patients presented exanthema, shortly after the peak of fever. A striking finding was the severe leukopenia, observed in the vast majority of patients (51/69 (73.91%) who were tested on the initial visit to the hospital). The white blood cell count ranged from 1000 to 12 000 cells/μL (mean, 4028; SD, 1849), with 40–60% neutrophils. C-reactive protein was in the normal range. Nine patients had fever for more than 1 week (one for 22 days).

TABLE 1. Clinical signs and symptoms and underlying diseases in the 95 patients with West Nile non-neuroinvasive disease who visited the Giannitsa General Hospital during the West Nile virus outbreak in Greece, 2010

	N (%)
Clinical signs and symptoms	
Fever	93 (97.89)
Fatigue	84 (88.42)
Headache	79 (83.16)
Arthralgia/myalgia	76 (80.00)
Anorexia	63 (66.32)
Exanthema	61 (64.21)
Dizziness	43 (45.26)
Nausea/vomiting	43 (45.26)
Stiff neck	32 (33.68)
Ataxia	21 (22.11)
Tremor	19 (20.00)
Diarrhoea	21 (22.11)
Respiratory symptoms	2 (2.11)
Underlying diseases	
Hypertension	7 (7.37)
Diabetes mellitus	6 (6.32)
Heart failure	3 (3.16)
Psoriasis	1 (1.05)
Cancer	1 (1.05)
Chronic obstructive pulmonary disease	1 (1.05)

Symptoms resolved after 3–10 days (mean, 5 days); however, 13 (13.7%) patients continued to have symptoms for a longer time (1–2 months). A slight tremor was observed in the patients with the more severe form of the disease. Tremor and transient parkinsonism have been reported in previous studies, and it was suggested that involvement of the basal ganglia may be characteristic for WNV infection [10,11].

Although West Nile fever is considered to be a mild disease, many of the patients suffered greatly. The following are some of their statements: 'I thought I would die'; 'I had never been so heavily ill before'; 'I was unable to make a single step'; and 'I felt like I was being hit with a hammer'.

The fact that no fatalities were observed among these patients, together with the presence of rash in 64.21% of cases, as compared with 10.34% (3/29) in WNND patients, among whom the fatality rate was 34.5%, suggests that rash might have a favourable effect regarding severe disease and mortality in WNV disease. Rash as a marker of good prognosis has been highlighted previously [12]. The involvement of diverse target host cells and the release of various cytokines and cytotoxic factors, resulting in differences in immune response, might explain the variations in clinical signs and symptoms, and the severity and outcome of the disease.

Patients were previously in good health, and only few of them had an underlying disease (Table 1). Resurgence of psoriasis was seen in one patient, suggesting that WNV further suppresses immune deficiency.

In conclusion, WNNND, a common type of WNV infection, constitutes a distinct clinical syndrome that should not always be considered a 'mild disease'.

Acknowledgements

We would like to thank all patients who participated in the study. The study was financially supported by the Hellenic Centre for Disease Control and Prevention.

Transparency Declaration

No conflicts of interest.

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