West Nile virus encephalitis in kidney transplanted patient, first case in Hungary: Case report

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Abstract: The complications caused by the rarely viral infections are more frequently treated in ICU (intensive care unit). The world paid attention to the WNV (West Nile virus) infections only in 1999, when 62 meningoencephalitis were registered in New York State. Six cases of WNV occur annually in Hungary. The authors present the first transplanted Hungarian patient with WNV encephalitis. The patient was hospitalized with epigastric pain, diarrhea, continuous fever, and decreasing amount of urine. The first checkup of infectious diseases was without any result. Although using of empirical antimicrobal therapy, the multiorgan failure patient remained febrile. On the basis of clinical signs, meningitis or encephalitis was suspected despite negative results of repeated cultures. On the 8th day, WNV infection was confirmed by serological examinations. With intravenous immunoglobulin therapy used within confines of supportive treatment, the patient became afebrile. After 21 days in ICU with good graft function, the patient was moved to the ward and he left the hospital after two more weeks. Until now, no prophylactic or etiological treatment has been developed for WNV. The early treatment is done with immunoglobulin or interferon; otherwise therapy has only supportive function. The disease caused by virus is more aggressive in transplanted patients and could be caused death.

Keywords: West Nile virus, encephalitis, kidney transplantation, intravenous immunoglobulin therapy, case report

Introduction

The rarely viral infections, the complications caused by them are more frequently treated in the ICU (intensive care unit): flu, respiratory *syncytial* virus, varicella zoster, cytomegalovirus, Epstein-Barr virus, adenovirus, severe acute respiratory syndrome. The structure, transmission, or immunological background of the pathogen could play a major role in the variety of the clinical picture or the disease's outcome [1]. Nowadays, the epidemics are more frequently caused by pathogens which are not so well known. The world paid attention to the WNV (West Nile virus) infections only in 1999, when 62 cases of meningoencephalitis were registered in New York State. At present, there is no kind of etiologic treatment or prophylaxis developed against the WNV. The infection caused by the WNV is by far more aggressive in solid organ transplanted patients, with higher mortality [2, 3]. The early goal-specific treatment is performed with immunoglobulin and interferon; otherwise the therapy is mainly supportive.

Case Report

A 52-year-old uremic patient had a first kidney transplantation in 1994 for which chronic allograft nephropathy developed, and hence the patient received the second kidney transplantation in 1998 (the first graft was not removed). In October of 2008, the patient was admitted at the department of transplantation because of fever >39 °C associated with epigastrial pain, diarrhea and oliguria. The early goal-specific therapy was done according to the international guidelines for management of severe sepsis and septic shock (empirical antibiotic therapy – moxifloxacin completed with the reduction of the immunosuppressive drugs dose – cyclosporine and mycophenolat mofetil). The different analyses of cultures, laboratory tests, chest X-ray, and abdominal ultrasound result were negative. The continuously febrile patient's health condition, especially the neurological status, deteriorated in spite of the treatment. The patient was transferred at the ICU on the fourth treatment day with Cheyne–Stokes breathing, a

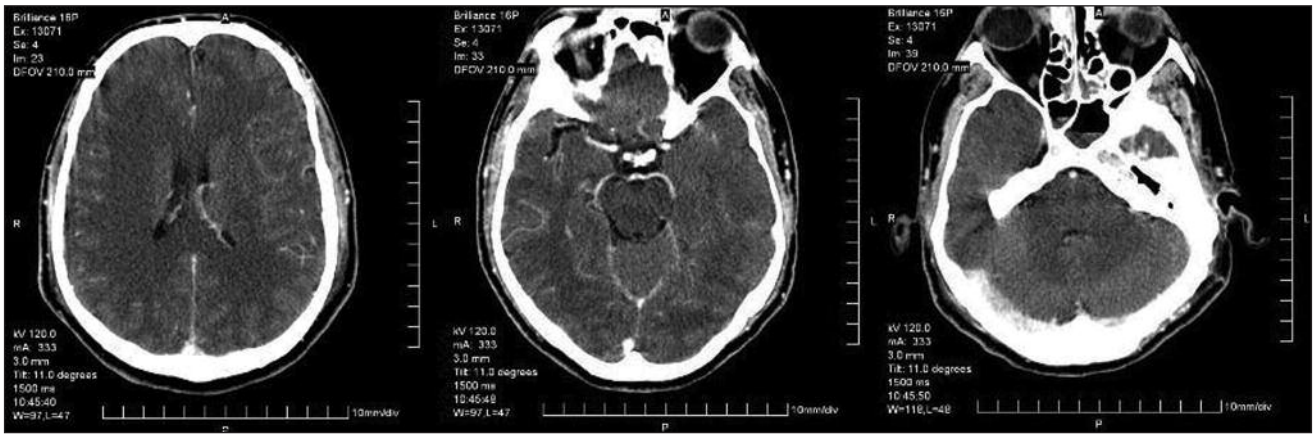

Fig. 1. Tighter liquor space, else a negative cranial CT scan

SOFA (Sequential Organ Failure Assessment) score: 11, an APACHE II (Acute Physiology And Chronic Health Evaluation) score: 14, and Glasgow Coma Scale: 2–3–3; mechanical ventilation was started with invasive hemodynamic monitoring.

The empirical antibiotic therapy was switched on (meropenem, ampicillin-sulbactam, metronidazole) and was completed with antifungal and antiviral therapy (acyclovir, fluconazole). The immunosuppressant therapy was converted first to prednisolone (30 mg/day), then to hydrocortisone mono-therapy (200 mg/day). Using a total body computer tomography (CT) scan done to detect the reason for septic-toxicity, only the primary graft was found morbid, and hence graftectomy was performed. The pathological examination found severe graft impairments: total glomerular destruction, and effusion with chronic inflammation. The patient's health condition did not improve postoperatively; besides rising inflammatory tests and continuous fever, a neck restriction movement occurred. The second cranial CT scan was negative apart from the tighter liquor spaces (see *Fig. 1*).

The bacterial meningitis was excluded by the neurological examination, and the analysis of the liquor, but the viral or fungal etiology, was postulated. In the absence of known pathogen (repeated cultures, viral screenings with negative result), intravenous immunoglobulin therapy was started (Pentaglobin®, Biotest). The patient shortly became afebrile, and hence after five days of treatment this was stopped. In the course of the serological investigation, increasing titers of specific WNV antibody (IgG ≥ 1:10 and IgM ≥ 1:320) were detected from both serum and liquor.

Cerebral magnetic resonance imaging (MRI) investigation was done on the 10th treatment day without any pathological findings; the electroencephalography performed justified right hemisphere and mesodiencephalon functional disorder. Parallel to the applied treatment, the patient's health condition improved rapidly, he regained consciousness, the inflammatory parameters returned to normal, and he was successfully extubated on the 11th treatment day. The patient was transferred after 20 ICU treatment days to the nephrology department from where he departed home with good graft function and without any neurological deficit after two more weeks of follow-up care (WNV-specific IgG titer ≥ 1:320). Throughout, the patient had a good graft function with the steroid mono-therapy; the original combined immunosuppression was applied on 23th treatment day (see *Fig. 2*).

The origin of WNV infection remained obscure, the patient did not receive blood component transfusion, and he was not in direct contact with birds or domestic animals. The WNV check up was performed also to the members of his family with negative result. Therefore, it is supposed that the source of WNV encephalitis was mosquitoes.

Discussion

The WNV was discovered in 1937 in the West Nile territory of Uganda. The infection spread from Africa to the Near-East, then to Europe, and afterwards to the rest of the world. Between 1937 and 1990 a smaller number of infections with moderate fever were reported, but after 1990 several thousand of WNV infections were registered (Romania, 1996; Russia, 1999; Israel, 2000; United States, 2002; Canada, 2002) [4]. In Hungary, according to the available data, annually only few WNV infections are registered. Between 2003 and 2010 an average of 10 illnesses per year were reported, but the number of WNV cases are changing year by year. In the organ transplantation field, our reported kidney transplanted patient is the first verified WNV case in Hungary (2008).

The WNV is a positive RNA virus and belongs to the Flaviviridae family, *Flavivirus* genus. Actually, two genetically different West Nile viruses are well known, the human infections are caused by both of them. The primary carriers are the wild birds; however, different domestic animals (horse, dog) which live in the human neighborhood could also be infected with the virus [4]. The vectors of the pathogen are different mosquitoes

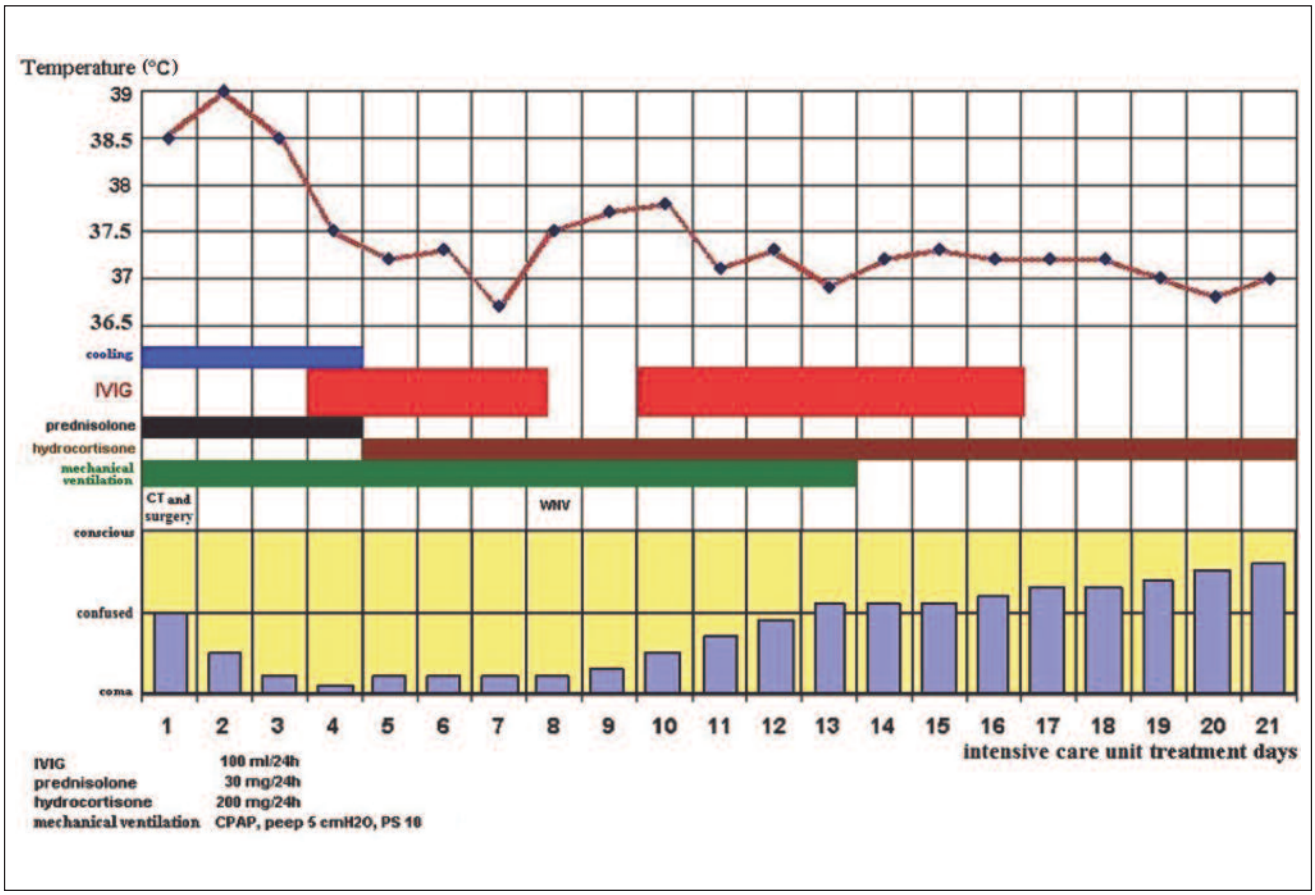

Fig. 2. Improvement of the clinical condition as the result of the treatment applied in West Nile virus-induced encephalitis. IVIG: intravenous immunoglobulin

species *(Culex)* that mostly pass the virus in the bird–mosquito–bird cycle. The humans get in the cycle only accidentally. The epidemic yearly cycle is determined by the mosquitoes activity – this is usually between July and October. The virus spreads from human to human only accidentally by blood component transfusion, organ transplantation, or across the placenta and by breast feeding [5, 6]. The infection incubation time is between 2 and 14 days, and in 20% of the infected only moderate fever (3–6 days) is developed. In the mild form of the infection, weakness, malaise, lack of appetite, sickness, emesis, ocular pain, headache, muscular pain, and swelling of lymphatic glands can occur, but the upper respiratory catarrh is also common. In 0.1–0.5% of the patients, an aggressive form of the infection could be seen with meningitis, encephalitis, and flaccid paresis or paralysis. The unconsciousness is accompanied often with cranial nerve inflammation, epilepsy, rarely with chorioiditis, vitritis and chorioretinitis. In the cases reported in literature, there are also severe complications of the WNV infection like myocarditis, pancreatitis and fulminant hepatitis [4].

It is important to emphasize that in the presence of immunosuppression the incubation time is longer: about 3 weeks; the course of the disease could be: 1–2 weeks; the frequency of severe neurological infection is much higher: 40% and it could lead to a fatal end. The cause of death can occur by neuronal dysfunction, cerebral edema and respiratory insufficiency [5].

The WNV infection can be diagnosed by detecting antiviral antibodies (IgM and IgG) or viral RNA (nucleic acid amplification testing) from the blood or liquor [7]. The IgM is detectable after the first week of disease and remains positive 6 months after WNV infection. Unfortunately, there is an antigen similarity in the *Flavivirus* genus and this can cause positive IgM serological result for a brief period after yellow fever vaccination. The organ and blood donor's screening by detecting the specific antiviral antibodies is not a routine procedure [8]. The liquor characteristic alteration is pleocytosis, neutrophilia and increased proteins [9]. The cranial CT scanning and MRI investigation usually are negative, rarely is thickening of the meninx or the lesion of the thalamus, pons, cerebellum and basal ganglions found [10–12]. The disease has no vaccination prophylaxis or specific treatment; therefore, the therapy is mainly supportive. Certainly, there are investigations with several antiviral products such as purine, pyrimidine analogues, or alpha, beta interferon or intravenous immunoglobulin [2, 5]. The role of immunoglobulin in the WNV infection therapy is not proved; nevertheless, based on different recovery case reports it may be presumed that the treatment is efficient

and in the absence of a specific therapy at present it is the single applicable treatment possibility [3].

The animal WNV infection experiments have demonstrated that apart from the cytotoxic T lymphocytes, the humoral response also has a crucial role in the early phase of the disease [3, 11]. Similar animal experiments have proved that intravenous immunoglobulin products made from healthy Israeli people blood provide 100% defense against WNV infection depending on dosage and treatment time. On the contrary, the intravenous immunoglobulin products made from healthy US people blood have 0% defense property [13, 14].

In summary, in the case of an unknown etiology or a therapy-resistant fever, it is worthwhile to extend the screening also to WNV. The 2008 United States protocols advise the exclusion of WNV infection in every febrile transplanted patient or in the presence of immunosuppression [15]. The lesson of this case justifies the need of WNV investigation in febrile transplanted patients also in Hungary as well. According to the animal experiments and recovery case reports, in the early phase of the disease, the 10 days treatment with intravenous immunoglobulin products is beneficial.

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