West Nile Virus Neuroinvasive Disease Accelerating Probable Dementia With Lewy Bodies

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Abstract: We describe a case of dementia with Lewy bodies immediately following encephalitis due to West Nile virus (WNV). The patient had rapid eye movement–sleep behavior disorder (RBD), and parkinsonism. It shares its neuropathologic hallmark with Parkinson disease with or without dementia, namely the presence of Lewy bodies, which contain α-synuclein (Asyn). It is believed that DLB and Parkinson disease are different expressions of the same underlying pathology, α-synucleinopathy. We describe a case of probable DLB immediately following encephalitis due to West Nile virus (WNV) and discuss the pathologic link between both diseases.

Key Words: dementia with Lewy bodies, West Nile virus, encephalitis

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Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia, after Alzheimer disease. Its clinical core features are recurrent visual hallucinations, fluctuating cognition, acting out of dreams due to rapid eye movement–sleep behavior disorder (RBD), and parkinsonism. It shares its neuropathologic hallmark with Parkinson disease with or without dementia, namely the presence of Lewy bodies, which contain α-synuclein (Asyn). It is believed that DLB and Parkinson disease are different expressions of the same underlying pathology, α-synucleinopathy. We describe a case of probable DLB immediately following encephalitis due to West Nile virus (WNV) and discuss the pathologic link between both diseases.

CASE REPORT

A 66-year-old Macedonian man with a history of arterial hypertension was hospitalized after a holiday in Serbia for high fever at 40°C since 7 days, followed since 3 days by a permanent confusional state and agitation alternating with hypersomnolence. The patient complained of myalgia, was disoriented in time and space, and did not recognize his family. At the emergency ward, he had a body temperature of 37.6°C and blood pressure of 188/10 mg/dL. Leukocytosis [14.93×10³ white blood cells (WBCs)/μL, N: 3.5 to 11 WBCs/μL], neutrophilia (80.6%, N < 75%), and low lymphocytes (9%, N: 20% to 45%), and C-reactive protein 39.5 mg/mL (N < 10.0 mg/dL). Cerebrospinal fluid (CSF) analysis showed hyperproteinorrachia (1.27 g/L, N < 0.45 g/L), normal glucose, high lactate (4.44 mmol/L, N < 2.44 mmol/L), and 117 WBCs/μL (N < 5 WBCs/μL), with 81% lymphocytes. CSF culture was negative for aerobic and anaerobic germs, mycobacteria, yeasts, and fungi. Detection of herpes simplex 1-2, enterovirus, and varicella zoster virus by polymerase chain reaction was negative in the CSF. Serology for syphilis, hepatitis B and C, human immunodeficiency virus, herpes simplex, Epstein-Barr virus, cytomegalovirus, and tick-borne encephalitis was negative for an acute infection. Blood antigen for Cryptococcus neoformans was negative.

Immunoglobulin (Ig) M for Borrelia was positive in plasma and CSF but doubtful by the Western blot, which was attributed by the laboratory to the presence of nonspecific IgM, wherein IgG was negative and remained negative after 1 month.

IgM and IgG serology was positive for dengue and WNV. As IgG for WNV remained positive when controlled with another assay (neutralization), the patient fulfilled the diagnostic criteria of confirmed neuroinvasive arboviral disease. The serology for dengue was considered as a cross-reaction.

Electroencephalography showed diffuse slowing with a main activity of 5 to 6 Hz. The patient was hospitalized and treated empirically with ceftriaxone, ampicillin, and acyclovir. Fever disappeared, but the patient had fluctuating cognition with disorientation in time, dysexecutive problems, and anxiety. Montreal Cognitive Assessment with a Macedonian translator was 16/30. CSF control after 1 month showed 15 WBCs with 88% lymphocytes, a hyperproteinorrachia of 1.22 g/L, lactate 2.79 mmol/L, a protein tau of 849 pg/mL (N < 247 pg/mL), normal β-amyloid1–42 (> 509 pg/mL, N > 469 pg/mL), and normal p-tau (35 pg/mL, N < 61 pg/mL).

In the months after hospitalization, the patient still had important cognitive problems (Montreal Cognitive Assessment 18/30, with deficits in word fluency, abstraction, attention, and short-term and long-term memory) and a marked irritability treated with sertraline 50 mg/d. Nine months after the initial symptoms, the patient developed visual hallucinations, nocturnal agitation with acting out of dreams, and paranoid delusions. His wife reported the presence of RBD and constipation before the infection occurred.

Ilofיחp-ne-123 scan showed a bilateral striatal hypofixation. The diagnosis of probable DLB was made according to the diagnostic criteria of the Fourth Consensus Report. RBD improved markedly with an evening dose of 0.5 mg clonazepam, while agitation and hallucinations disappeared almost entirely with donepezil 10 mg/d.

DISCUSSION

WNV is a mosquito-transmitted single-stranded RNA (arthropod borne) arbovirus of the family Flaviviridae. Up to 80% of infections are subclinical and hence underreported. Several species of mosquitoes can transmit the disease, especially Culex pipiens, which feeds on birds in which the virus particles are carried and amplified. Incubation is probably between 3 and 14 days followed by a febrile illness that lasts 3 to 6 days. Central nervous system...
(CNS) involvement, resulting in (meningo-) encephalitis or flaccid paralysis due to myelitis occurs in <1% of the infected patients, advanced age being the most important risk factor. WNV encephalitis has a mortality of 10% to 20%, while 70% to 75% of the survivors have persistent deficits from months to years after infection, including fatigue, insomnia or excessive sleepiness, muscular pain and weakness, headache, movement disorders, and behavioral and cognitive changes.

The most efficient diagnostic method is detection of serum or CSF IgM antibodies, although cross-reactions are possible with other flaviviruses such as dengue, Japanese encephalitis, and Saint Louis encephalitis.

The link between WNV infections and neurodegenerative diseases has been reviewed recently. WNV accesses the CNS either by endothelial passive transport, by using leukocytes as a "Trojan horse," by retrograde axonal transport after infection of peripheral nerves, or by leaking into tight junctions that are weakened by tumor necrosis factor-α-induced peripheral inflammation. In the latter case, arterial hypertension, as was present in our patient, can help weakening the blood-brain barrier. The virus replicates in astrocytes, microglia, and neurons, but can also damage neuronal cells by the resulting inflammatory reaction and gliosis.

Inoculation of cultured mouse striatal neurons with WNV doubles the expression of Asyn after 2 to 24 hours. The same group found an increased intensity of Asyn in the subcortical gray matter from patients with acute WNV encephalitis and proved that Asyn knockout mice with WNV encephalitis had a higher mortality rate (95%) than mice expressing Asyn (25%). The authors conclude that Asyn protects neurons against infection with WNV and other RNA viruses, by limiting viral growth and by reducing virus-induced caspase-3 activation, which would lead to cell death.

According to his wife, rare episodes of RBD and constipation were already present in our patient before he developed WNV encephalitis. RBD is characterized by complex motor behavior and vocalizations during rapid eye movement–sleep and is a strong and early predictor of synucleinopathy. Almost all patients with idiopathic RBD develop neurologial disease, mostly synucleinopathies, in the decade after onset of RBD. Constipation is one of the many factors that significantly increase the risk of dementia and parkinsonism in patients with RBD (hazard ratio: 1.67). Therefore, it is very likely that our patient would have ultimately developed DLB even without WNV infection, but that the viral encephalitis accelerated phenotypical conversion to DLB due to an augmented expression of Asyn. Fortunately, definite diagnosis was not possible, as it requires autopsy.

CONCLUSIONS

This case report illustrates the potential role of RNA viruses in the pathogenesis of synucleinopathies. Data about WNV exposure in synucleinopathies are lacking but might help elucidating the complex and multifactorial pathogenesis of these invalidating disorders. Physicians should be aware of the possibility that chronic neurologological cognitive and behavioral symptoms after WNV neuroinvasive disease can be the consequence of a synucleinopathy rather than the infection itself, and can be symptomatically treated with cholinesterase inhibitors.

REFERENCES