West Nile Virus: An Emerging Threat in Transplant Population

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Abstract

West Nile virus (WNV) has become one of the new challenges for transplant programs. In addition to transmission by mosquito bite, interhuman transmission is possible through blood products or organ transplantation. Majority of WNV infections present as asymptomatic or mild febrile illness, with less than 1% of infected developing neuroinvasive disease. Many studies report naturally acquired or donor-derived WNV infections in solid-organ transplant recipients, mainly kidney, but also liver, heart, lungs and pancreas. Given the much higher risk of neuroinvasive disease (40% and even higher) based on serologic and clinical studies and increased mortality in transplant population, WNV infection should be considered in all patients presented with fever and neurological symptoms after transplantation, especially during the arbovirus transmission season.

Keywords: West Nile virus, mosquito, immunology, neuroinvasive disease, encephalitis

CURRENTLY, WEST NILE VIRUS (WNV) is one of the most widely distributed emerging arboviruses. In the last decade, WNV infections are continuously reported in many parts of the world. In the United States, the annual number of disease cases varied from 712 to 5674 (Centers for Disease Control and Prevention; CDC 2019), while in Europe, the number of WNV disease cases ranged from 74 to 262 (European Centre for Disease Prevention and Control; ECDC 2019). In the 2018 transmission season, European Union Member States and neighboring countries have reported the highest number of cases so far with a total of 2083 human WNV disease cases and 181 deaths (ECDC 2019).

In nature, WNV is maintained in a bird-mosquito-bird cycle, while humans represent incidental or “dead-end” hosts. However, interhuman transmission is possible through blood products or organ transplantation (Centers for Disease Control and Prevention; CDC 2002).

Although majority of WNV infections are asymptomatic (~80%) or present as a mild self-limited febrile illness (20%), less than 1% of infected persons develop neuroinvasive disease (meningitis, encephalitis, and myelitis). Ad-

vanced age, immunosuppression, and comorbidities, such as cancer, hypertension, diabetes, and cerebrovascular disease, are risk factors for neuroinvasive infection and long-term sequelae (O’Leary et al. 2004, Murray et al. 2006, Vilibic-Cavlek et al. 2019). Mortality in patients with neuroinvasive disease may reach up to 10% (Sejvar 2016).

Transmission of WNV by organ transplantation was first reported in 2002 (CDC 2002, Iwamoto et al. 2003). Serologic and clinical studies estimate that the risk of neuroinvasive disease in transplant patients infected with WNV is 40% and even higher (Table 1) than in the general population (1%) (Kumar et al. 2004a). In addition, WNV is associated with an increased mortality in the transplant population. In one case series of 11 transplant recipients, a mortality rate of 18% and a high incidence of neurological sequelae were reported, including mechanical ventilation dependence (Kleinschmidt-DeMasters et al. 2004). However, there are several reports of WNV neuroinvasive disease after solid-organ transplantation (SOT) with a complete recovery (Hardinger et al. 2003, Desalvo et al. 2004, Saquib et al. 2008) and asymptomatic WNV infections as well (Rabe et al. 2013, Winston et al. 2014).

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TABLE 1. WEST NILE VIRUS INFECTIONS IN SOLID-ORGAN TRANSPLANT RECIPIENTS

<i>Transplanted organ</i>	<i>Country</i>	<i>Year</i>	<i>Patients</i>	<i>Age, years</i>	<i>Mode of transmission</i>	<i>Clinical manifestations</i>	<i>Outcome</i>	<i>References</i>
Kidney	USA	2002	2	Adult, 31	Organ transplant	Meningoencephalitis	Improved	Iwamoto et al. (2003)
		2002		Adult, 38	Organ transplant	Meningoencephalitis	Died	
	USA	2002	2	Adult, 43	Unknown	Meningoencephalitis	Died	DeSalvo et al. (2004)
		2002		Adult, 40	Unknown	Meningoencephalitis	Recovered	
	USA	2002	1	Adult, 38	Organ transplant	Meningoencephalitis	Died	Cushing et al. (2004)
	USA	2002	2	Adult, 51	Unknown	Encephalitis	Improved	Kumar et al. (2004b)
				Adult, 43	Unknown	Encephalomyelitis	Improved	
	USA	2002	2	Adult, 76	Mosquito bites	Meningoencephalitis	Recovered	Hardinger et al. (2003)
		2002		Adult, 42	Mosquito bites	Meningoencephalitis	Improved	
	USA	2002	1	Adult, 62	Blood products	Encephalitis	Died	Pealer et al. (2003)
	USA	2002	1	Adult, 54	Blood products	Encephalitis	Died	Shepherd et al. (2004)
	USA	2002	2	Adult, 54	Unknown	Meningoencephalitis	Recovered	Wadei et al. (2004)
		2003		Adult, 70	Unknown	Meningoencephalitis	Died	
	USA	2003	4	Adult, 50	Unknown	Meningoencephalomyelitis	Unknown	Kleinschmidt-DeMasters et al. (2004)
		2003		Adult, 59	Unknown	Meningoencephalomyelitis	Unknown	
		2003		Adult, 62	Unknown	Meningoencephalitis	Recovered	
		2003		Adult, 48	Unknown	Meningoencephalitis	Improved	
	USA	2003	1	Pediatric, 2.5	Mosquito bites	Meningoencephalitis	Recovered	Ravindra et al. (2004)
	USA	2004	1	Pediatric, 15	Unknown	Encephalitis	Recovered	Francisco et al. (2006)
	USA	2005		Adult, NA	Organ transplant	Asymptomatic infection	Recovered	CDC (2005)
		2005	1	Adult, 32	Unknown	Meningoencephalitis	Recovered	Saqui et al. (2008)
	USA	2005	1	Adult, 56	Mosquito bites	Meningoencephalitis	Died	Jain et al. (2007)
		2008	1	Adult, 52	Mosquito bites	Encephalitis	Improved	Smudla et al. (2011)
	Hungary						Died	Rabe et al. (2013)
	USA	2010	2	Adult, 73	Organ transplant	Encephalitis	Died	
				Adult, 52	Organ transplant	Asymptomatic infection	Recovered	
	Italy	2011	2	Adult, 33	Organ transplant	Meningoencephalitis	Unknown	Inojosa et al. (2012)
				Adult, NA	Organ transplant	Neuroinvasive disease	Unknown	
	USA	2011	1	Pediatric, 10	Mosquito bites	Meningoencephalitis	Recovered	Lambert et al. (2016)
	USA	2011	2	Adult, 59	Organ transplant	Encephalitis	Died	Winston et al. (2014)
		2011		Adult, 51	Organ transplant	Encephalitis	Recovered	Winston et al. (2014)
	USA	2012	2	Adult 51	Mosquito bites	Meningoencephalitis	Improved	Yango et al. (2014)
				Adult, 73	Mosquito bites	Meningoencephalitis	Died	
	Croatia	2013	1	Adult, 62	Mosquito bites	Meningoencephalitis	Improved	Santini et al. (2015)
	Turkey	Unknown	1	Adult, 25	Unknown	Meningoencephalitis	Recovered	Ertlav et al. (2014)
	USA	2015	1	Pediatric, 14	Mosquito bites	Meningoencephalitis	Recovered	Wilson et al. (2017)
	Italy	2016	1	Adult, 47	Unknown	Meningoencephalitis	Recovered	Zanoni et al. (2018)
	Croatia	2018	1	Adult, 59	Mosquito bites	Meningoencephalitis	Improved	Fares et al. (2018)
	Croatia	2018	1	Adult, 66	Mosquito bites	Meningoencephalitis	Improved	Unpublished; Project CRONEUROARBO
Liver	USA	2002	1	Adult, 71	Organ transplant	WNV fever	Recovered	Iwamoto et al. (2003)
	USA	2002	1	Adult, 47	Blood products	Encephalitis	Improved	Pealer et al. (2003)
	USA	2002	1	Adult, 58	Unknown	Encephalitis	Died	Kumar et al. (2004b)

(continued)

TABLE 1. (CONTINUED)

<i>Transplanted organ</i>	<i>Country</i>	<i>Year</i>	<i>Patients</i>	<i>Age, years</i>	<i>Mode of transmission</i>	<i>Clinical manifestations</i>	<i>Outcome</i>	<i>References</i>
	USA	2003	2	Adult, 50	Unknown	Encephalomyelitis	Improved	Kleinschmidt-DeMasters et al. (2004)
	USA	2003		Adult, 56	Unknown	Meningoencephalitis	Died	CDC (2005)
	USA	2005	1	Adult, NA	Organ transplant	Encephalitis, Flaccid paralysis	Unknown	Rhee et al. (2011)
	USA	2009	1	Adult, 51	Organ transplant	Encephalitis	Recovered	Rabe et al. (2013)
	USA	2010	1	Adult, 47	Organ transplant	Asymptomatic infection	Unknown	Morelli et al. (2010)
	Italy	2010	1	Adult, 25	Organ transplant	Asymptomatic infection	Recovered	Winston et al. (2014)
	USA	2011	1	Adult, 61	Organ transplant	Asymptomatic infection	Unknown	Inojosa et al. (2012)
	Italy	2011	1	Adult, NA	Organ transplant	Asymptomatic infection	Unknown	Unpublished; Project CRONEUROARBO
	Croatia	2018	1	Adult, 61	Blood products	Meningoencephalitis	Died	
	USA	2002	1	Adult, 63	Organ transplant	Meningoencephalitis	Recovered	Iwamoto et al. (2003)
Heart	USA	2002	1	Adult, 26	Unknown	Meningitis	Recovered	Kumar et al. (2004b)
	USA	2005	1	Adult, 56	Unknown	Encephalitis	Died	Bragin-Sánchez and Chang (2005)
	USA	2008	1	Adult, 62	Organ transplant	Encephalitis	Improved	CDC (2009)
Lungs	USA	2013	1	Adult, 20	Unknown	Encephalitis	Died	Gomez et al. (2015)
	Croatia	2013	1	Adult, 64	Mosquito bites	Meningoencephalitis	Improved	Santini et al. (2015)
	USA	2018	1	Adult, 69	Unknown	Myelitis	Died	Dong et al. (2018)
	Israel	2000	1	Adult, 42	Unknown	Encephalitis	Recovered	Hamdan et al. (2002)
	USA	2003	1	Adult, 61	Unknown	Meningoencephalitis	Recovered	Kleinschmidt-DeMasters et al. (2004)
	Canada	2003	1	Adult 49	Unknown	Meningoencephalitis	Improved	Hoekstra (2005)
	USA	2005		Adult, NA	Organ transplant	Encephalitis, Flaccid paralysis	Unknown	CDC (2005)
Pancreas Multiorgan	USA	2011	1	Adult, 59	Donor transplant	Encephalitis, Flaccid paralysis	Died	Winston et al. (2014)
	Italy	2011	1	Adult, NA	Organ transplant	Asymptomatic infection	Unknown	Inojosa et al. (2012)
	USA	2003	1	Adult, 37	Mosquito bites	Encephalitis	Recovered	Ravindra et al. (2004)
	USA	2003	2	Adult, 51	Unknown	Meningoencephalitis	Improved	Kleinschmidt-DeMasters et al. (2004)
	USA	2003		Adult, 32		Meningoencephalitis	Recovered	
	USA	2003	1	Adult, 44	Mosquito bites	Encephalitis	Improved	Ravindra et al. (2004)
	USA	2007	1	Adult, 45	Mosquito bites	Meningoencephalitis	Died	Koepsell et al. (2010)
Kidney+pancreas	USA	2012	1	Adult, 49	Unknown	Meningoencephalitis	Improved	Yango et al. (2014)

NA, not available.

There are many studies reporting donor-derived or naturally acquired WNV infections in the adult SOT recipients, mainly kidney, but also liver, heart, lungs, and pancreas. However, data on WNV infections in the pediatric SOT population are very limited (Table 1). As in the general population, it seems that risk of fatal neuroinvasive disease in the pediatric transplant population is lower compared to adults. Four reports describing post-transplant WNV meningoencephalitis in pediatric patients aged from 2.5 to 15 years showed a complete recovery in all patients (Ravindra et al. 2004, Francisco et al. 2006, Lambert et al. 2016, Wilson et al. 2017).

Detection of IgM antibodies in cerebrospinal fluid (CSF) and/or serum using enzyme immunoassay is currently the most sensitive diagnostic test for WNV infection. Because WNV IgM may not be positive until up to 8 days following disease onset, specimens collected less than 8 days after the onset may be negative for IgM, and testing should be repeated. In contrast, IgM antibodies may persist up to 500 days after primary WNV infection or even longer in some patients (Papa et al. 2011). Determination of IgG avidity may be helpful in these cases (Vilibic-Cavlek et al. 2018). Detection of WNV IgM in CSF strongly suggests acute infection, as IgM does not easily cross the blood–brain barrier. Due to high level of cross-reactivity between flaviviruses, the virus neutralization test is still the “gold standard” confirmatory testing for WNV infection (Di Gennaro et al. 2014). Other methods, including RT-PCR testing, can be helpful, but are significantly less sensitive than antibody tests and should be done in conjunction with serology. However, RT-PCR on serum, CSF, and urine samples may sometimes be the only method for WNV diagnosis in individuals who are unable to mount a detectable immune response such as transplant population (Koeppel et al. 2010).

There is no specific therapy against WNV available. Supportive treatment and reduction of immunosuppression are the first line of interventions in severe cases. Ribavirin, interferon alpha-2b, and immunoglobulins were considered in treating WNV disease with inconsistent results (Sejvar et al. 2003, Gea-Banacloche et al. 2004, Hart et al. 2014, CDC 2020). Potency of ribavirin and interferon alpha-2b was documented *in vitro*, although clinical efficacy was not established. Possible explanations for unfavorable outcomes could be related to drug and patients’ characteristics such as: high drug concentrations, limited drug penetration into central nervous system (CNS), a consequential toxicity, along with delayed drug application, older age, female gender, and comorbidities (Chowers et al. 2001, Anderson et al. 2002, Hart et al. 2014). Administration of intravenous immunoglobulins (IVIG) with high titers of WNV antibodies in early stage of the disease could provide favorable results. Animal studies suggest the effect of passive antibody transfer after virus has reached the CNS, but efficacy declines with time indicating that administration of immunoglobulins should be as early as possible (Shimoni et al. 2001, Ben-Nathan et al. 2003, 2009, Saquib et al. 2008, Makhoul et al. 2009, Morelli et al. 2010, Rhee et al. 2011). However, further clinical trials are needed to address the timing and route of IVIG administration, as well as their therapeutic efficacy.

In an attempt to improve transplant outcomes related to WNV disease, identification of infected organ and blood

donors is necessary in WNV endemic areas during increased WNV activity (Winston et al. 2014, Anesi et al. 2019). Although current recommendations and screening practices of organ donors for WNV are not harmonized, WNV nucleic acid amplification testing is recommended (Anesi et al. 2019). Deferral of organ donors with known WNV infection or recent fever or unexplained neurologic symptoms should be considered (Winston et al. 2014, Anesi et al. 2019).

In the post-transplant period, WNV infection may be prevented by avoiding mosquito bites. Patients should be counseled to avoid outdoor activities in the period of the highest mosquito activity, to use long sleeves and long pants, and to apply repellents on exposed skin (Anesi et al. 2019).

Furthermore, effective WNV vaccines for horses but no licensed vaccine for humans exist. Several clinical trials were conducted with promising results (Ulbert 2019). Implementation of a vaccine for high-risk patients may be feasible, whereas mass vaccination is not cost effective (Amanna et al. 2014).

In conclusion, WNV has become one of the new challenges for transplant programs worldwide. In light of the WNV emergence, clinicians should be aware that transplant recipients could be exposed to WNV through multiple sources, including direct infection from the bite of mosquitoes, transfusion of blood products, and graft from an infected donor. Therefore, WNV infection should be considered in all patients presented with fever and neurological symptoms after transplantation, especially during the arbovirus transmission season.

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