Chapter 17
West Nile Virus

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Core Message West Nile virus is the most common cause of arboviral encephalitis in the USA at this time. The virus, originally discovered in 1937 in Uganda in Africa, west of the Nile, was of low virulence initially causing only minor illnesses in humans; however, since then a more virulent strain had emerged and spread to most continents, causing epidemics of severe central nervous disease. The evolution and spread of West Nile virus was studied extensively since its emergence in the western hemisphere in 1999 and this has provided an opportunity to better understand the factors that contribute to viral mutation and migration.

1 Introduction

It has been more than a decade since the first human case of West Nile virus (WNV) in the Western Hemisphere was documented. Before 1999, WNV was almost unknown to the public in North America. Today, it is widely distributed in the USA and has been detected in all continents except Antarctica, making WNV one of the

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most widely distributed arboviruses in the world [1]. Viruses constantly mutate, strains that are more virulent emerge, and West Nile Virus is no exception.

With the well-deserved attention toward other high virulence viruses such as influenza A and human immunodeficiency viruses (HIV), West Nile virus is beginning to slip from the attention of the public and health care providers. At a time of reemerging viral threats, this arthropod-borne illness remains important. This review summarizes what is known about WNV since it was first reported in New York more than a decade ago.

2 Virology

2.1 Classification and Structure

West Nile virus belongs to the family *Flaviviridae*, genus *Flavivirus*. It is a single stranded, positive sense, enveloped RNA virus with a genome that is approximately 11 kb [2]. Other members of the *Flaviviridae* family that are major human pathogens include Japanese encephalitis virus (JE), Saint Louis encephalitis virus (SLEV), Dengue viruses 1–4, and yellow fever virus. The WNV genome contains nine major proteins that are implicated in replication and pathogenesis [3]. Three proteins are structural including the capsid protein (C) that binds viral RNA, a premembrane protein (prM) that blocks premature viral fusion, and a protein (E) that mediates viral attachment, membrane fusion, and viral assembly [3]. Five other proteins are non-structural (NS1, NS2A, NS2B, NS3, NS4A, and NS5) and those regulate viral transcription, replication and attenuate the host antiviral responses [4–9].

Two major Lineages of WNV, 1 and 2, have been described. Lineage 1 covers a large geographic area including Africa, Middle East, Southern Europe, Australia, Asia, and the Americas [10]. Lineage 1 is more pathogenic with the potential to cause severe central nervous system infection and death. Lineage 2 is mostly confined to sub-Saharan Africa and its pathogenesis in humans is relatively low, mostly causing self-limited febrile illness.

2.2 Genotype Introduced to Western Hemisphere

Studies have shown that WNV Genotype NY99 was responsible for the 1999 New York City outbreak and that it was in Lineage 1 [11]. The subsequent spread of WNV across North America, however, was caused by a new genotype "North American dominant" or WN02 that emerged from the NY99 strain [12, 13]. WN02 genotype is characterized by 13 conserved nucleotides changes, 1 of which results in an amino acid substitution, Valine to aniline in position 159 (V159A), in the envelope (E) protein. This single amino acid change was shown to decrease the incubation period of the virus in mosquitoes and increase the virulence of the virus,

hence increasing transmission, infectivity rates, and the severity of the infection and can be viewed as a successful adaptation of the virus in its new environment [13].

More recent genomic sequences studies demonstrate further evolution of WNV, and potential emergence of a new genotype in the southwestern USA (SW/WN03 genotype); however, further experiments are needed to investigate potential phenotypic changes that occur in conjunction with the genotype changes and to determine if the SW/WN03 genotype will replace the current dominant NA/WN02 genotype [12].

3 Epidemiology

3.1 Virus Journey and Spread

WNV was first isolated in the West Nile region of Uganda in 1937 from a woman with fever [14]. Soon after that, mosquito transmission among vertebrate hosts was elucidated. Although at that time, the virus caused only self-limited febrile illness it was noted to be serologically related to the previously identified neurotropic viruses, Japanese Encephalitis and Saint Louis encephalitis viruses (JE and SLEV).

Between 1950 and 1990, periodic outbreaks with mild self-limited febrile illness and rare central nervous system involvement were documented [1]. In addition, sporadic cases and larger outbreaks were documented in rural areas in the Middle East, Israel, and southern France. Moreover, a WNV subtype (Kunjin virus) was isolated in Australia. After 1990, the epidemiology of WNV changed further with larger epidemics in Romania, Russia, Tunisia, and Israel [1, 10]. These strains now manifest with severe CNS involvement and high mortality. The first outbreak in the Western Hemisphere occurred in Northeastern USA. In New York City in 1999, 62 cases of encephalitis were reported including seven deaths [16]. The strain causing the epidemic, denoted as NY99, was in lineage 1 and similar to a strain circulating then in Israel (Isr98) [17]. The specific mode of introduction of WNV to the USA is still unknown, although infected birds are thought to be the most likely vehicle of transport. Possible theories of introduction include infected bird migration, illegal or legal importation of vertebrate hosts or vectors, intentional introduction as a bioterrorism attempt, or less likely by an infected human host [11, 17]. Soon thereafter the Virus rapidly spread across the continent, reaching the Pacific coast in less than 3 years (Fig. 17.1). By 2003, more than 2,000 cases of CNS disease and 200 deaths were reported in the USA. Although, since then, the incidence started to decline, mostly due to improved control measures, there are still more than 1,000 neurological cases per year. One interesting epidemiological phenomenon is that WNV appears to be displacing SLEV in its ecosystem in parts of western USA. WNV and SLE virus exploit the same avian host and vector species; however, the NS3 helicase mutation present in the WNV genotype confers elevated virulence for avian hosts and appears to have provided WNV a competitive advantage in this region [18, 19].

Fig. 17.1 Map showing origin and migration of West Nile Virus. Data to create Map obtained from [1, 10, 22]

Cases of WNV have also been reported in Canada. In addition, enzootic transmissions occurred in the Caribbean and Central America. Of note WNV activity has not been reported in tropical South America as yet. This may be due to cross-protection from other flaviviruses circulating in tropical regions, less competent arthropod and avian hosts than in temperate regions, and the greater diversity of host species in the tropics or reduced virulence of WNV in the tropics [1, 20]. Similarly, there have been no overt cases in the UK, although there is evidence of serological conversion in sentinel chickens. However, since the year 2000, WNV has been detected regularly in France, in the southern regions, with significant morbidity in horses. The lack of human cases in northern Europe, compared to southern Europe, may possibly be attributed to the feeding behavior of the predominant vector, *Culex pipiens* that exists as two strains in North Europe. One strain feeds primarily on humans and the other strain feeds on birds only, whereas hybrid mosquitos feed on both hosts in Southern Europe facilitating viral transmission [1, 21]. Additional factors, such as climate, likely play an important role in viral transmission; for example lower temperatures in northern Europe are not usually suitable for the development of large populations of competent mosquitoes capable of effective viral transmission to humans [22].

The dynamic relationship between vectors and hosts, including mosquito feeding and avian migratory patterns, has facilitated the distribution of WNV as one of the most widespread arboviruses in the world (Table 17.1). Currently WNV has been reported on all continents, with the exception of Antarctica. In North America alone, there are approximately 59 species of mosquitoes (predominantly the *Culex* species) and 284 species of birds that have been reported as having been infected

Table 17.1 Summary of epidemiology of WNV

Year	Geographical location	Viral strain	Clinical properties
1937	Uganda—region west of the Nile	WNV of lineage 2	WNF; low virulence virus.
1937–1949	Africa, Eurasia, Australia and the Middle East	WNV of lineage 2	Sporadic cases of disease and outbreaks of WNF mostly in rural population; low virulence virus.
1950–1990	Egypt and the upper Nile delta	WNV of lineage 2	Epidemics of WNF with rare CNS disease; low virulence virus.
1990–1998	Middle east, Romania, Southern Europe and Australia	Emergence of WNV of lineage 1, WNV subtype (Kunjin virus) was isolated in Australia	Frequent outbreaks associated severe disease including viral encephalitis, now with case-fatality rate of nearly 10 %; high virulence virus.
1999–2003	New York city, USA, Israel, Russia, and Tunisia	WNV of lineage 1, (NY99)	Outbreaks occurred now in major metropolitan cities with CNS disease and a case fatality rate of about 10 %; High virulence virus.
			Virus spread to Canada and parts of South America.
2003–2011	Virus spread across continental USA reaching endemicity level with periodic out breaks.	New genotype had arisen, denoted as North American or WN02 from, the 1999 introduced (NY99) genotype and had displaced the introduced virus.	Seasonal (Summer) outbreaks with CNS disease in about 1 % of infections and mortality of about 10 %. The WN02 dominance appears to be related to increased transmission efficiency in *Culex* spp. mosquitoes.

Summarized from [1, 10, 22]

with WNV. The virus is maintained in nature in an enzootic cycle between birds and mosquitoes. Some mammals (such as horses and squirrels) and reptiles (such as alligators) have also been shown to be viremic [1].

3.2 Virus Transmission

The majority of human infections are due to mosquito bites. Humans and many other vertebrates are accidental hosts with low-grade, transient viremia insufficient to infect mosquitoes and are considered “dead-end” hosts. The amplifying hosts are birds including crows (*particularly Corvus brachyrhynchos*), jays, blackbirds, finches, warblers, and sparrows, which generally remain asymptomatic. Crows and blue jays are particularly susceptible. Indeed, increased mortality in such birds can predict increased risk for human cases and can be a crude indicator of virus activity [23].

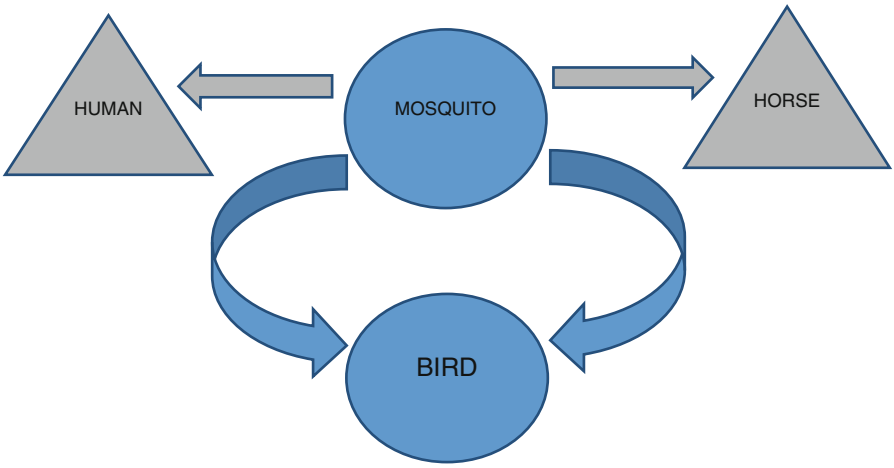

Fig. 17.2 West Nile Virus Transmission; the virus is maintained in nature in an enzootic cycle between birds and mosquitoes. Some mammals (such as humans and horses) are accidental "dead end" hosts

The *Culex* mosquito appears to be the most important mosquito species in the enzootic cycle, although the species varies by geographic location. Transovarial transmission of the virus in mosquitoes likely provides for viral over-wintering. After female mosquito takes a blood meal from an infected bird, the virus penetrates the gut, replicates, and travels to the mosquito's salivary glands. Then during subsequent feedings, mosquito injects virus-laden saliva into warm-blooded hosts and the cycle continues. Transmission season is more often from July to September. Multiple factors influence WNV transmission and infectivity, including advanced age, host immune and genetic susceptibility, and behavioral and environmental factors. Mortality among patients with meningitis and encephalitis is approximately 10 % and often in the elderly. The most significant outbreaks described in the 1990 serologic survey showed that severe complications are infrequent with only 1/150 infections resulting in WNV meningitis or WNV encephalitis. From data up to 2007, it has been estimated that from the 11,000 cases reported of invasive neurological disease in the USA that 1.6 million person were most likely infected. Serological surveys indicate that even in areas experiencing outbreaks, less than 10 % of the population is infected with WNV [24–29].

Rare but documented routes of viral transmission include transplantation of infected organs, the use of infected blood products, transplacentally, and possibly, through breast milk [30, 31]. At the peak of the 2002 epidemic in the USA, the risk for infection by transfusion was estimated to be as high as 21 per 10,000 donations [30]. Since then, blood-screening using real-time polymerase chain reaction (PCR) has been instituted and has significantly decreased the risk for contaminated blood.

Up to 2012 in the USA there were more than 37,000 reported (>350,000 estimated) human cases and over 1,500 (mostly in neuroinvasive cases) reported deaths since it was first detected in New York in 1999 [33] (Table 17.2).

Table 17.2 West Nile virus disease cases and deaths reported to CDC by year and clinical presentation, 1999–2012

Year	Neuroinvasive disease cases	Neuroinvasive disease deaths (%)	Non-neuroinvasive disease cases	Non-neuroinvasive deaths (%)	Total cases	Total deaths (%)
Total	16,196	1,443 (9)	20,892	106 (1)	37,088	1,549 (4)
2012	2,873	270 (9)	2,801	16 (1)	5,674	286 (5)
2011	486	42 (9)	226	1 (<1)	712	43 (6)
2010	629	54 (9)	392	3 (1)	1,021	57 (6)
2009	386	32 (8)	334	0 (0)	720	32 (4)
2008	689	41 (6)	667	3 (<1)	1,356	44 (3)
2007	1,227	117 (10)	2,403	7 (<1)	3,630	124 (3)
2006	1,495	162 (11)	2,774	15 (1)	4,269	177 (4)
2005	1,309	104 (8)	1,691	15 (1)	3,000	119 (4)
2004	1,148	94 (8)	1,391	6 (<1)	2,539	100 (4)
2003	2,866	232 (8)	6,996	32 (<1)	9,862	264 (3)
2002	2,946	276 (9)	1,210	8 (1)	4,156	284 (7)
2001	64	10 (16)	2	0 (0)	66	10 (15)
2000	19	2 (11)	2	0 (0)	21	2 (10)
1999	59	7 (12)	3	0 (0)	62	7 (11)

Source: CDC; ArboNET, Arboviral Diseases Branch, Centers for Disease Control and Prevention http://www.cdc.gov/westnile/resources/pdfs/cummulative/99_2012_CasesAndDeathsClinicalPresentationHumanCases.pdf

Although patients with WNV disease reported onset of illness throughout the year, more than 90 % of patients had onset of illness during July to September. The annual epidemic peak in the USA consistently occurs in August [33]. WNV has become endemic in the USA, with ongoing potential for seasonal epidemic transmission at the local, regional, or national level. Although annual WNV disease incidence varies substantially, the pattern of recurrence indicates that transmission is likely to continue [33].

4 Pathogenesis

WNV is maintained in nature in an enzootic cycle of mosquito-bird-mosquito. Mosquitoes serve as maintenance vectors in the cycle. The most common mosquito species responsible for transmitting WNV is the *Culex* species but this varies with geographic area. Of these, *Cx pipiens molestus*, *Cx univittatus* and *Cx tarsalis* have been implicated as important vectors of transmission in Africa, Middle East and the outbreaks in the USA [34]. Birds serve as amplifying hosts and usually remain asymptomatic, despite continuous viremia; however, occasionally high levels of viremia will lead to the bird's demise. Studies have shown a higher incidence of WNV infections in humans residing in high avian mortality areas, as avian mortality rates correlate with West Nile virus activity [23, 35]. The exact pathogenesis of

WNV in humans is not yet well understood but animal studies have shed some light into the interaction of the virus and the host immune system. Following *Culex* mosquito inoculation, the virus replicates in Langerhans *dendritic* cells and then disseminate to the regional lymph nodes where replication continues [36]. WNV then spreads to other peripheral organs including liver and spleen via the blood stream. As the virus is recognized by innate and adaptive immune responses, replication is limited in the periphery in most cases. Interferon-alpha and beta restrict viral translation and replication early in infection [37–41]. Both the humoral and cell-mediated immune systems are important in virus control [36].

Early CNS spread and high viremia are limited by B cells and primary IgM antibodies in conjunction with the complement systems. Specific activation of complement via innate recognition of proteins and secreted antibody interacts with a wide range of cell surface receptors on myeloid, lymphoid, and stromal cells [42–44]. Interferon-gamma-producing gamma-delta T cells also play a role in controlling viral replication, by stimulating the adaptive immune response. CD4 and CD8 T cells help viral clearance in the peripheral tissues [45–47]. If this peripheral control of the virus is inadequate, the virus travels to the CNS, via the blood or by retrograde axonal transport, where neuronal bodies are the primary target. In the CNS, INF alpha and beta with the aid of chemokines CXCL10 and CCL5 are responsible for controlling WNV infection and prolonging neuronal survival [37, 41, 48].

West Nile virus utilizes multiple mechanisms to survive, infect, and evade immune system recognition. Some of these mechanisms include the capacity to induce rapid cell death, diverse cellular tropism including the immune cells of the peripheral blood that may also serve in the early dissemination of the virus, masking of the virus RNA from the immune cells and the capacity to induce IFN resistance [49–51].

Human genetic factors are thought to influence the severity and outcome of the infection. For example in humans a 32-bp deletion in the coding region of the CC chemokine receptor 5 (*CCR5Δ32*) was reported to be associated with both increased susceptibility to WNV infection and death [52]. Certain single nucleotide polymorphisms (SNPs) of the genes that encode the antiviral enzyme 2′–5′ oligo-adenylate synthetase (OAS), *OAS1* and *OASL*, were found to be associated with WNV susceptibility or WNND [53]. Similarly, genetic SNPs in the interferon regulatory factors (*IRF3* and *MX1 genes*) alter the human interferon response to the virus pathway and were found to be associated with symptomatic WNV infection and disease progression [52].

5 Clinical Manifestations

WNV disease is a nationally notifiable disease with standardized case definitions. State and metropolitan heath departments report cases to CDC through ArboNET, an electronic passive surveillance system. The spectrum of WNV disease ranges from asymptomatic (~80 %) to neuroinvasive disease with morbidity and mortality of about 10 % of cases [10, 54]. When symptoms occur, they develop after an incubation period that typically lasts 2–6 days but may extend to 14 days, or even longer in immunosuppressed persons.

5.1 West Nile Fever

Roughly 20 % of those exposed to the virus develop West Nile Fever (WNF), symptoms of which include sudden onset of an acute, nonspecific, influenza-like illness lasting 3–6 days, with high fever, chills, malaise, headache, backache, arthralgia, myalgia, and retro-orbital pain, without overt neurologic signs [55]. In addition, generalized lymphadenopathy and a maculopapular or pale measles-like rash were reported. Incidence of rash is about 50–15 % of the cases, reported more frequently in children than adults and in WNF than with neuroinvasive disease which may point to a more robust host immune response to the virus. The rash usually presents approximately 5 days after the onset of symptoms, and lasts for about 1 week. Hepatomegaly, splenomegaly, myocarditis, pancreatitis, and hepatitis have also been described occasionally in severe WN virus infection [56].

5.2 West Nile Neuroinvasive Disease

Less than 1 % of those infected develop West Nile Neuroinvasive Disease (WNND), which may include encephalitis, meningitis, or meningo-encephalitis and flaccid paralysis (poliomyelitis-like syndrome) [10, 54]. WNND more frequently affects the elderly and immunocompromised population [57]. Patients typically have a febrile prodrome of 1–7 days, which may be biphasic, before developing neurological symptoms. Although in most cases, the prodrome is nonspecific, 15–20 % of patients have features suggestive of WN fever, including eye pain, and or a rash and about 5 % have lymphadenopathy [58, 59].

5.2.1 Meningitis and Encephalitis

Of those exhibiting WNND, roughly 40 % develop meningitis and 60 % encephalitis. Clinical features of meningitis include fever, nuchal rigidity, photophobia, headache, retro-orbital pain, and cerebrospinal fluid pleocytosis [55, 58, 59]. On the other hand, signs and symptoms such as altered mental status, focal weakness/numbness, seizures, or visual disturbances and diagnostic evidence of brain parenchymal involvement point towards the diagnosis of encephalitis [56].

5.2.2 Acute Flaccid Paralysis

Acute flaccid paralysis (poliomyelitis-like) caused by virus infection of the anterior horn of the spinal cord (myelitis) has been recognized and once paralysis is established, little long-term improvement has been described. Paralysis is frequently asymmetrical and may be associated with meningoencephalitis. Other neurological features include cranial neuropathies, optic neuritis, and ataxia. Stiffness, rigidity, spasms, bradykinesia, and tremors, associated with basal ganglia damage, have also recently been recognized in WNND [56–58] (Table 17.3).

Table 17.3 Clinical Manifestations of WNV infection

West Nile Fever:
Fever, chills, Flu-like illness; myalgia, arthralgia, retro orbital pain. Rash, lymphadenopathy, hepatomegaly, splenomegaly, myocarditis, pancreatitis, hepatitis.
West Nile Neuroinvasive disease (*1 % of infections*):
Flaccid (polio-like) paralysis
Meningitis syndrome
Encephalitis syndrome
Seizures
Extrapyramidal signs (tremors, ataxia, Parkinson's' like features)
Optic neuritis

Summarized from CDC; West Nile clinical evaluation
http://www.cdc.gov/westnile/healthCareProviders/healthCareProviders-ClinLabEval.html

6 Diagnosis

Diagnosis of West Nile virus infection (WNF and WNND) is based on clinical presentation, and confirmed with serologic or nucleic acid amplification testing [33, 60].

6.1 Clinical Criteria

Clinical Criteria for Diagnosis of Neuroinvasive disease requires the presence of fever and at least one of the following in the absence of a more likely clinical explanation: (1) acutely altered mental status (e.g., disorientation, obtundation, stupor, or coma), (2) other acute signs of central or peripheral neurologic dysfunction (e.g., paresis or paralysis, nerve palsies, sensory deficits, abnormal reflexes, generalized convulsions, or abnormal movements), or (3) pleocytosis (increased white blood cell concentration in cerebrospinal fluid) associated with illness clinically compatible with meningitis (e.g., headache or stiff neck) [33].

Non-neuroinvasive disease requires, at a minimum, the presence of fever, the absence of neuroinvasive disease, and the absence of a more likely clinical explanation for the illness. Involvement of non-neurologic organs (e.g., heart, pancreas, or liver) should be documented using standard clinical and laboratory criteria [33].

6.2 Laboratory Criteria

Laboratory Criteria for Diagnosis of neuroinvasive disease include at least one of the following: (1) Isolation of virus from or detection of specific viral antigen or genomic sequences in tissue, blood, cerebrospinal fluid, or other body fluid by PCR or (2) Detection of virus-specific immunoglobulin M (IgM) antibodies

demonstrated in cerebrospinal fluid by antibody-capture enzyme immunoassay (EIA); or (3) A fourfold or greater change in virus-specific serum antibody titer; or (4) Virus-specific IgM antibodies demonstrated in serum by antibody-capture EIA and confirmed by demonstration of virus-specific serum immunoglobulin G (IgG) antibodies in the same specimen or a later specimen by another serologic assay (e.g., neutralization or hemagglutination inhibition) [33].

Probable cases of infection have (1) a stable (twofold or smaller change) but elevated titer of virus-specific serum antibodies or (2) virus-specific serum IgM antibodies detected by antibody-capture EIA but with no available results of a confirmatory test for virus-specific serum IgG antibodies in the same or a later specimen [33].

On average IgM and IgG develop rapidly after WNV viremia (about 4–7 days respectively) and viral RNA persist for about 2 weeks before becoming undetectable [61]. IgM may persist for 3–6 months and IgG will persist for many years, likely conferring immunity against new WNV infections [62].

Some trends in basic laboratory tests, although non-specific, may point towards West Nile Virus infection. For example, elevated white blood cell count (greater than 10,800/mm^3, but rarely greater than 20,000/mm^3), mild decrease in hemoglobin (less than 13.5 g/dL in males and less than 12.0 g/dL in females), hyponatremia (less than 135 mm/L), elevated creatinine kinase, abnormal liver function tests (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin), or transiently elevated lipase (usually asymptomatic) [57].

Cerebrospinal fluid shows a moderate lymphocytic pleocytosis (greater than 5 cells/mm^3 or a mean cell count of approximately 225/mm^3), with up to half the patients have a neutrophil predominance and sometimes there are no cells [55, 57]. The protein is moderately elevated (greater than 40 mg/dL), and the glucose ratio is typically normal.

Radiologically, in most cases of WNND Magnetic resonance imaging shows high signal intensities in the deep gray matter of the nervous system. Such abnormal signals can be found in thalamus, basal ganglia, mesial temporal structures, brain stem, cerebellum and the spinal cord [63]. Patients with WNND may sometimes have normal neuroimaging studies [57, 63].

As mentioned above, studies that definitively diagnose or confirm WNV infection includes viral isolation, amplification of viral nucleic acid and antigens with polymerase chain reaction, or enzyme-linked immunosorbent assay to detect WNV IgM or IgG antibodies [10, 33, 54]. It is to be noted however that some WNV-infected patients have persistent WNV IgM serum and/or cerebrospinal fluid after recovery without ongoing disease and hence interpretation of serological tests needs to be done carefully in conjunction with the clinical syndrome and careful consideration of other deferential diagnosis especially in cases of atypical presentation [64].

Other diagnostic studies include electroencephalography for patients with seizures and electromyogram studies for nerve conduction abnormalities [57]. These studies, although sensitive, are less specific than the traditional serologic studies mentioned above. Electroencephalograms show diffuse slowing and, in some cases, focal seizure activity. Nerve conduction studies typically show the reduced motor axonal

Table 17.4 West Nile Neuroinvasive disease diagnosis

Clinical criteria	Laboratory criteria	Other tests
Fever and	– *Isolation of virus* (specific viral antigen or genomic sequences in tissue by PCR, blood, cerebrospinal fluid); or	– Brain MRI: abnormal signals in the basal ganglia, thalamus, cerebellum, and brainstem.
– Acute confusion, or Acute signs of central or peripheral neurologic dysfunction (e.g., paresis or paralysis, nerve palsies, convulsions, or abnormal movements).	– Virus-specific immunoglobulin M (IgM) antibodies demonstrated in CSF or blood, or	– Nerve conduction studies show reduced motor axonal amplitudes.
– CSF pleocytosis consistent with viral meningitis syndrome	– A fourfold or greater change in virus-specific serum immunoglobulin G antibody titer.	

Summarized from: CDC. Surveillance for human West Nile virus disease—United States, 1999–2008. Surveillance summaries. MMWR April 2, 2010;59(SS02);1–17

amplitudes consistent with anterior horn cell damage, although there may also be some slowing of conduction velocities and some changes to sensory nerves [57, 65]. Nerve conduction studies are helpful to differentiate WNND from Guillain-Barre syndrome (Table 17.4).

7 Treatment

There is no current approved specific treatment for West Nile Virus infection. The current recommendation is supportive treatment. Yet three major therapeutic approaches are leading the research in finding a definitive treatment for this disease. These are Interferons, Ribavirin and intravenous Immunoglobulin.

7.1 Interferons

Interferon Alpha has been shown in vitro to be efficient in inhibiting WNV replication. It protects, restricts and enhances cellular and neuronal response to WNV infection [37]. Although some studies have shown that virulent WNV of lineage one, exhibits inherent resistance to interferon Alpha and Beta [41], Kalil, et al reported two cases of successful neurologic improvement after treatment with interferon Alpha 2b when given within 72 h of presentation [66]. On the other hand, there have been case reports showing ineffectiveness and poor outcomes with patients treated with interferon during an outbreak in Israel [67]. The therapeutic role of interferons is yet to be established.

7.2 Ribavirin

Some in vitro studies indicated that high doses of Ribavirin in animal model can be protective against the effects on WNV on the animal cell [68]. Ribavirin is an antiviral agent that Inhibits replication of RNA and DNA in wide range of viruses (nonspecific) and can be associated with serious side effects in high doses. Ribavirin in some animal studies was shown to be associated with increased mortality in the context of WNV infection and hence there is not yet a consensus of the efficacy and safety of this drug in WNV infection in humans [69].

7.3 Intravenous Immunoglobulins

The use of intravenous immunoglobulins for WNV infections is also under research with the rational that high titers of WNV antibodies can mount a protective effect against the WNV [70, 71]. Several clinical trials are underway for the treatment of WNV. Nevertheless, to date studies showing efficacy and responses to these different therapies in humans remain inconclusive and treatment remains mostly supportive.

8 Prognosis

The prognosis of WNV infection appears to be variable but favorable in general, depending mostly on the presentation ranging from West Nile fever to neuroinvasive disease. The most common symptoms post-infection were fever and fatigue lasting for several days. Aching, general malaise, and weakness lasting weeks to months were reported in some series [58, 64, 72]. The prognosis of patients with WNV meningitis and encephalitis, is also generally favorable but persistent headaches, fatigue, focal neurological deficits may persist for months to years [73]. Important predictive risk factors such as age, use of immunosuppressants, and persistent comorbidities play an important role in the overall outcome [29, 74, 76, 77].

Longitudinal cohort studies of long term outcome and prognosis of WNV infected individuals showed that on average physical and mental function as well as mood and fatigue, appear to return to normal within 1 year of symptom onset. Patients with WNND took slightly longer to recover, and the recovery rate of meningitis and encephalitis cases were about the same. Patients without preexisting comorbidities had faster recovery of physical function [76]. A slower recovery rate is associated with WNV paralysis (poliomyelitis-like syndrome) where recovery was found to be much slower and sometimes rare [78, 79].The overall case-fatality rate with WNND is about 9–10 %; highest in older individuals and those with comorbidities [76].

9 Vaccination and Prevention

WNV has caused, and certainty has the potential to cause, large epidemics of arboviral illness in the Western Hemisphere. Consequently, the need for efficient modes of prevention and the development of a human vaccine are mandatory. At this time the most effective prevention methods remain as mosquito avoidance, vector control and personal protection measures [79]

Mosquito repellants, elimination of breeding sites and barrier methods such as window screens are emphasized during epidemic seasons.

Previous efforts for the early detection and monitoring of WNV activity have used dead bird density or spatial scan statistic as a proxy for transmission risk for humans [80]. Another, perhaps more accurate, approach is the DYCAST system (The Dynamic Continuous-Area Space-Time system). This is a biologically based spatiotemporal model that uses statistical and geographical analysis of public reports of dead birds to identify areas at high risk for West Nile virus transmission to humans, implemented in New York City in 2001 and Chicago, IL in 2002 [81]. Results from prospective implementation of the DYCAST system in California showed that this model provided accurate and early identification of areas at high risk for human WNV transmission during an epidemic in 2005, and was used to assist public education campaigns, surveillance, and mosquito control programs [73, 82]. Early warning of high-risk areas for West Nile Virus activity allows preventative measures to be implemented in a timely and effective manner.

Public health education programs should target older adults, people who are immunosuppressed and those with co morbidities, because they are at increased risk for neuroinvasive disease and death. In the absence of an effective human vaccine, the cornerstones of WNV disease prevention will continue to be (1) community-level mosquito control (larviciding, adulticiding, and breeding-site reduction), (2) peridomestic measures (repairing and installing door and window screens, using air conditioning, and reducing breeding sites), and (3) personal protection measures (use of repellents, use of protective clothing, and avoidance of outdoor exposure when mosquitoes are most active). WNV surveillance continues to be important for monitoring seasonal WNV activity and targeting prevention and control activities [33].

The improved screening of banked blood with the use of Minipool nucleic-acid amplification testing (MP-NAT) and Individual Donation NAT (ID-NAT) significantly reduced WNV transmission via blood transfusion [83].

A major emphasis remains to produce a human vaccine. Although no human vaccine is available yet, the future remains optimistic, given the substantial impact made in veterinary public health with the currently licensed four equine WNV vaccines in the USA. These include a formalin-inactivated virus, a recombinant Canarypox virus expressing prM/E proteins of WNV [84]. A chimeric virus vaccine from an infectious clone of yellow fever 17D virus [85], and a DNA vaccine, the first DNA vaccine to be licensed in any country [86]. Promising data regarding a human vaccine is being analyzed since reports of results of a phase one human clinical trial in subjects receiving WNV DNA vaccine documented the development of

neutralizing antibodies to the WNV [87]. If a human vaccine becomes available and in conjunction with proper preventions methods, the risk of WNV infection and its complications can be substantially be reduced.

10 West Nile Virus and Bioterrorism

There has been growing concern about the use of microbes as weapons for a number of reasons [88, 89]. First, microbes have the potential of killing or harming a large number of people in a short period of time. Second, their deliberate spread can be hidden or go unnoticed until large numbers of people get sick and present to hospitals, emergent care facilities, and doctors' offices. Third, even the slightest suspicion of a bioterrorism attack, can cause significant panic and havoc among people and have significant financial consequences. Fourth, bioweapons are relatively inexpensive to create and sometimes referred to as the "poor man's atomic bomb." Finally yet importantly, as the power of biological sciences grow it seems inevitable that more potent and diverse bioweapons will be created. West Nile Virus can be targeted for such use; it is moderately easy to disseminate by infected mosquitoes and birds, has moderately high virulence with significant morbidity and mortality with CNS disease and has the potential of even higher virulence with genetic manipulation. As matter of fact, when the virus first appeared in the USA the US government and the CDC have considered the act of bioterrorism, but further investigations showed that the virus activity was consistent with its natural behavior. It is believed that the introduction of the virus was work of nature by bird migration or accidental by imported infected birds. It is important however to understand the potential of using WNV as a bioterrorism agent and physicians in the USA should be familiar with the various clinical presentation and means of diagnosing illnesses caused by West Nile Virus [90].

11 Global Warming and West Nile virus

There are several indications that the rising temperatures of the planet had aided the spread of vector borne infections, including WNV [22]. Similar to other arboviral diseases, the spread of the virus is influenced by vector spread. Climate, such as temperature and rain fall have significant impact on vectors' geographic habitats, life cycles, feeding behavior, and evolution. As mentioned above, nucleotide sequencing studies have showed that WNV introduced to New York in 1999 (NY99) was closely related to a strain of WNV from Israel (Isr98) at the time. The weather in New York during the spring and summer of 1999 had been particularly warm and humid which favored intensive mosquito breeding and efficient arbovirus transmission, resulting in the epidemic [22, 91, 92]. WNV then evolved and adapted to its

new environment and is now expected to continue to be an endemic virus with frequent outbreaks in the USA [92]. Climate change is a current global concern and its consequences on health and human diseases should be regarded with greater importance and urgency.

12 Conclusion

West Nile virus is one of the most widely distributed of all arboviruses in the world and has been reported in all continents except Antarctica. West Nile Virus belongs to the family Flaviviridae together with Japanese encephalitis viruses (JE), Saint Louis Encephalitis viruses (SLE), Dengue and Yellow fever viruses. The virus is maintained in nature in an enzootic cycle of mosquito–bird–mosquito with humans and other vertebrates as incidental dead end hosts. The journey of West Nile virus from Africa where it was first discovered, in Uganda west of the Nile, in 1937 till it reached the Western hemisphere in 1999, has been intriguing, interesting and exemplifies the evolution and migration of viruses. To date, globally, there are over 350,000 estimated human cases and in the USA, approximately 37,000 cases reported with 1,500 deaths. The incidence has since declined due to improved vector control efforts, but is still detectable, making WNV an endemic pathogen to the USA, with the potential of forming seasonal epidemics (July to September). Currently, WNV is the most common cause of arboviral CNS infection in the USA. Up to 80 % of human infections however are asymptomatic. Both of the humoral and cell-mediated immune systems are important in controlling the virus, and are usually efficient and terminate the virus in the peripheral organs in the majority of immune-competent individuals. The virus however is neurotropic and in certain high-risk individuals (elderly or immunocompromised) can cause devastating neurological disease with mortality approximately around 10 %. Other milder presentations include West Nile fever, which presents as a self-limited Flu-like illness. Diagnosis is confirmed serologically or by PCR technology and treatment is supportive at this time. Prevention is by vector control and personal protective measures against mosquitos bite. Vaccines for veterinarian use are available and has significantly reduced incidence in horses. Vaccines trials for human are under way and are promising. Although it is less likely that the introduction of the virus to the western hemisphere is a deliberate act of bioterrorism and more likely to be accidental or work of Nature, the potential for the West Nile Virus to be weaponized is there and should not be ignored by the health care establishment. The changing climate effect on the spread of arboviral viruses, exemplified by WNV, is evident, cannot be ignored and should be regarded with greater urgency.

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