West Nile Virus: An Historical Overview

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ABSTRACT

West Nile virus (WNV) has quickly established itself in North America since its recognition in New York City in 1999. Historically, WNV has been associated with temporally dispersed outbreaks of mild febrile illness. In recent years, the epidemiology and clinical features of the virus appear to have changed, with more frequent outbreaks associated with more severe illness being noted. The 2002 outbreak in North America was unprecedented in terms of the number of cases and geographic spread of the virus. Historical patterns of WNV provide few indications as to the future behavior of WNV in North America.

The emergence of West Nile virus (WNV), a flavivirus within the Japanese encephalitis antigenic complex, in New York City in the summer of 1999 marked the first time that this Old World virus had been identified outside of the Eastern Hemisphere (1). Within a 3-year period, the virus expanded its range in North America from a 6-county area around metropolitan New York City to the West Coast of the United States, establishing itself in 44 states and the District of Columbia, as well as in five Canadian provinces. In particular, the 2002 season saw an unprecedented number of human cases and a dramatic geographic spread (2). While recent assessments have led to a better understanding of the clinical, ecological, and epidemiological facets of WNV, an understanding of the historical patterns of WNV may provide additional insight into the current epidemic in North America.

BACKGROUND

WNV was first isolated from a febrile patient from the West Nile district of Northern Uganda in 1937 (3). The patient presented in the setting of a large epidemiologic study of yellow fever virus; however, inoculations of mice with the patient's serum resulted in the isolation of a virus with physical and pathologic properties similar to those of two flaviviruses, St. Louis encephalitis virus and Japanese B encephalitis virus, and sharing immunological relationships with these viruses. Although the index patient presented with fever only, these first studies with the newly discovered virus indicated that pathology primarily involved the central nervous system (CNS), suggesting its neurotropic nature.

The epidemiology and ecology of WNV was first characterized in detail during several outbreaks in the Mediterranean basin in the early 1950s and 1960s (4). The first recognized epidemic of WNV occurred in Israel in 1951 in a small town outside of Haifa, where a total of 123 cases with no fatalities occurred among 303 inhabitants (5); young children represented the majority of cases. During this outbreak the various clinical features associated with infection were first described in detail, with the main symptoms being fever, headache, myalgias, anorexia, abdominal pain, exanthems, and vomiting; lymphadenopathy, angina, and diarrhea were somewhat less common.

Several large outbreaks in Egypt between 1951 and 1954 led to a further understanding of the ecology, epidemiology, and clinical characteristics of WNV (4,6). On the basis of the detection of WNV in the blood of several children and a high seroprevalence rate among residents of a village north of Cairo in 1950, an extended study of WNV was begun in 1951 in the upper Nile Delta region (6). The studies included serosurveys among humans and animals; isolation and identification of virus vectors; experimental infection of birds, equines, arthropods, and humans; and ecologic assessments. Findings from the studies greatly increased the understanding of the various clinical and epidemiologic aspects of the virus. Serosurveys demonstrated that WNV was endemic along the Nile, with seroprevalence rates approaching 60%. Older children and adults appeared to have higher seroprevalence, while younger children seemed to have more symptomatic illness, suggesting that WNV was mainly an infection of early childhood. Infections were characteristically self-limited, febrile illnesses with rare occurrences of meningitis or encephalitis.

Serosurveys conducted among animals suggested that the virus was infectious in a wide range of species, including birds and non-human mammals. WNV-neutralizing antibodies were prevalent in birds, particularly crows. WNV was found to be infectious

in a number of non-human mammals but was particularly prevalent in equines, in which infection was frequently symptomatic and often fatal. The vector-borne nature of the virus had been suggested several years earlier (7) on the basis of ecology and transmission studies. In addition, the discovery in Egypt that the virus could be isolated only from mosquitoes, and not from other arthropods, suggested mosquitoes as the primary vector; this was substantiated by the demonstration that only mosquitoes could maintain a vector cycle by infection of a host through feeding, followed by subsequent transmission through biting (6). Mosquitoes of the *culex* species appeared to be the primary vectors.

During the Egyptian investigations, a series of experimental infections of humans demonstrated important aspects of the dynamics of human viremia (8, 9). At the time, persons with incurable neoplasms were sometimes inoculated with viruses causing pyrogenic infection in an effort to inhibit the growth or spread of the cancer. Two separate series of patients were assessed after inoculation with WNV; in the vast majority of these patients, fever was the only clinical feature, although some patients developed clinical encephalitis. These experimental infections also suggested that the virus could be detected in blood as soon as 24 hours after infection, and viremia could persist for 6 to 12 days, and perhaps longer. It also appeared that the persistence of viremia correlated with the severity of illness.

In 1957, an outbreak of WNV occurred in Israel, where severe neurologic manifestations among a group of elderly nursing home residents became the first reports of such neurologic events among humans (10). Prior to this, neurologic illness had rarely been reported, and only among patients undergoing experimental infection. However, during subsequent outbreaks, including France in 1962 and South Africa in 1974, patients developing meningitis or encephalitis were recognized (11, 12). Neurologic manifestations appeared to be infrequent, however, and the vast majority of symptomatic patients still appeared to develop mild, self-limited febrile disease. Of note is the South African outbreak of 1974, during which thousands of febrile illness cases were documented, with only one case of encephalitis noted (13). Subsequent similar outbreaks continued to occur sporadically, including epidemics in Russia, Spain, South Africa, and India (13). Large outbreaks of WNV were very infrequent throughout the late 1970s and 1980s.

WEST NILE VIRUS SINCE 1996

Beginning around 1996, the epidemiology and clinical spectrum of WNV appeared to change. A large outbreak of WNV occurred in the area around Bucharest, Romania, and was notable for a number of reasons (14, 15). It was the first WNV outbreak to be centered in a predominantly urban area, and it was the first outbreak of the virus in which the preponderance of symptomatic cases involved CNS infection (15). The Romanian outbreak was extensively studied and suggested several things about the changing epidemiology of the virus. The overall seroprevalence rate among Bucharest residents during the epidemic period was around 4%, and little predilection for any particular age group, sex, or geographic location in the city was noted (14). Serum samples obtained from Bucharest residents that predated the epidemic suggested that, for the most part, the population in and around the city was serologically naive to WNV and thus highly susceptible. Epidemiologic studies suggested that certain factors prevalent in the rather deteriorated urban infrastructure of Bucharest contributed to the epidemic, including a profusion of areas conducive to mosquito breeding, an abundance of amplifying hosts in the form of domestic fowl, and the absence of protective barriers, such as screens on windows and doors (15). Although cases of milder febrile illness concomitant with the outbreak of CNS infection were not observed, it was noted that surveillance was rather insensitive and may have been unable to detect such cases (15).

Following the 1996 outbreak in Romania, several subsequent epidemics associated with relatively high rates of CNS infection were observed throughout the Middle East and Europe, including Morocco in 1996, Tunisia in 1997, and large outbreaks in Italy and Israel in 1998 (13). Thus, it appeared that outbreaks of WNV were occurring more frequently; in addition, these outbreaks were associated with higher rates of severe CNS disease and higher fatality rates, predominantly among older individuals. The Tunisian outbreak of 1997 involved 173 patients hospitalized with meningitis or meningoencephalitis, and 8 deaths; more than half of all these patients were over 50 years of age (16). A large outbreak of WNV occurring in the Volgograd region of Russia during the early Summer of 1999 involved 183 serologically confirmed cases, with 84 cases of acute meningoencephalitis and 40 fatalities. In this outbreak, over 75% of the fatalities occurred in patients older than 60 years (17).

ARRIVAL OF WNV IN NEW YORK CITY

By the time the virus was first detected in North America in 1999, it had already had a recent history of more frequent outbreaks and more severe illness. In late August of 1999, a cluster of severe cases of encephalitis was noted in an area around Queens in New York City (18). An epidemiologic investigation by the New York City Department of Health identified eight such cases, and revealed that all of the patients had been previously healthy, had resided within the same 16 square mile area, and had recently engaged in outdoor activities. All but one had developed severe acute flaccid paralysis in the setting of encephalitis. As the initial suspicion

was that of an arthropod-borne virus (arbovirus) encephalitis, early testing was directed at common eastern North American arboviruses. Early serologic testing displayed IgM antibodies against St. Louis encephalitis virus by enzyme-linked immunosorbent assay.

Both before and during the human encephalitis investigation, an epizootic among birds associated with a high fatality rate had been noted in and around New York City (19). These were initially felt to be unrelated to the human epidemic. Pathologic assessment of the dead birds displayed involvement of multiple organs, including evidence of encephalitis; however, common avian pathogens were not detected (20). Genomic analyses using polymerase chain reaction and genome sequencing with specimens from New York City birds, infected mosquitoes collected in Connecticut, and human brain tissue from a fatal case of encephalitis, as well as expanded serological testing of specimens from suspected human cases identified WNV as the etiologic agent of this outbreak 4 weeks after the outbreak in humans was first reported to New York City public health officials (21-24). By the end of the Summer of 1999, 62 patients with serologic evidence of acute WNV infection, including 59 hospitalized patients, had been identified. Similar to more recent outbreaks of the virus, the epidemic seemed to be associated with a high rate of CNS involvement and a preponderance of cases in patients older than 60 years (25).

Although the mechanism of the introduction of the virus into North America remains unknown, it seems clear that the source of the WNV strain detected in New York City originated in the Middle East. A similar avian epizootic among domestic geese in Israel during 1997 and 1998 had been attributed to WNV (21, 26). Human cases of WNV occurred simultaneously in Israel and New York in August of 1999, and when the genomic sequences of WNV isolates or infected human brain tissue from the New York City outbreak were compared to various non-US strains, the greatest homology was found with a WNV strain isolated from a goose from the Israeli 1998 epizootic and subsequently with a strain detected in the brain tissue of an Israeli patient who died of West Nile encephalitis in 1999 (21). In addition, both the pattern of high avian mortality previously not associated with WNV outbreaks and the severity of human CNS disease seen in New York City and in Israel were similar during the 1999 outbreaks.

The introduction of WNV in North America was followed by progressive spread throughout the US. During the Summer of 2000, 21 cases of human WNV illness occurred among 10 counties in northeastern states (27). The following year, 66 cases were detected among a much more widespread geographic area, involving 38 counties in 10 states. The spread of human cases seemed to follow avian deaths; thus, avian death surveillance and, to a lesser extent, mosquito pool surveillance became important parts of public health efforts to track the virus and predict potential human cases (27). In addition to avian and human illness, a substantial number of equine cases were documented throughout the US, a pattern also being observed in other parts of the world. Large epizootics, particularly among equines, were noted in Italy in 1998 and 1999 (28) and in France in 2000 (29). However, these outbreaks did not seem to be associated with significant human disease. Human cases appeared to be relegated to Israel, Russia, and the US.

During the summer of 2002, however, the number of WNV cases in North America was unprecedented. This was the largest outbreak of West Nile meningoencephalitis ever recorded anywhere, and also the largest outbreak of arboviral meningoencephalitis ever documented in the western hemisphere. WNV expanded its geographic range from the Mississippi River area at the conclusion of the 2001 season to the Pacific Coast by the end of 2002. As of January 2003, the provisional human case count from the 2002 season was 4156, including 2354 cases of meningoencephalitis and 284 deaths (2). Particular regions of the US including parts of Louisiana, Mississippi, and the Chicago area, saw particularly high numbers of cases. Severe CNS disease continued to be predominantly seen in older individuals, but more cases of milder febrile illness in younger patients were detected, possibly as a result of enhanced surveillance efforts. The factors contributing to the magnitude of the 2002 epidemic remain unclear, but it is interesting to note that in several areas of the country, climatic and geographic factors during the Spring and Summer of 2002 were very similar to those in 1975, when a large epidemic of the related flavivirus, St. Louis encephalitis virus, occurred in the US (30). The particular factors and an understanding of how they may have contributed to or facilitated these large arboviral outbreaks require further elucidation.

COMMENT

The arrival and subsequent spread of WNV throughout North America serves as an example of how an "emerging" infectious disease may quickly and efficiently establish itself in a new environment. The reason for the increase in frequency and severity of outbreaks of WNV since 1996 remains unclear. The movement of the virus into areas with large immunologically naive populations, with an age structure including many elderly and immunocompromised individuals, may account in part for this observation (1); however, a more virulent strain of the virus has been suggested as well (31).

The future epidemiology of WNV in North America is uncertain, and the historic pattern of the virus provides little guidance as to its potential course in the US. Whether continued infection among the population will lead to a

decline in susceptible avian and human hosts, with a subsequent decline in the number of cases, remains to be seen. Following the large outbreak in 1996, Romania continued to experience cases during following years, although at greatly diminished rates, and seroprevalence rates among avians appeared to remain high (15). Comparison with the epidemiologic patterns of other related flaviviruses may be illustrative: St. Louis encephalitis tends to occur sporadically in various regions of the US, with the appearance of occasional larger clusters and, rarely, large geographically dispersed epidemics (32). On the other hand, Japanese encephalitis tends to be a hyperendemic disease in areas of Southeast Asia, where symptomatic illness predominates in serologically naive children (33). The fact that WNV illness in the US seems to predominate in adults and the elderly, with children less frequently developing symptomatic illness, may suggest that a substantial immune population will develop over time; however, the future pattern cannot be predicted.

During the period of WNV transmission in North America, arbovirus surveillance capacity has been increased substantially; however, the complex epidemiology of the illness and the difficulties associated with serologic testing for the virus continue to present challenges for surveillance and prevention measures. Efforts to control and reduce vector populations, reinforcement of public health messages of personal protection from mosquitoes, and vigilant surveillance and public awareness campaigns are likely to remain the cornerstones of the public health response to WNV. Through continued surveillance and further study, it is hoped that the remaining questions regarding the epidemiologic and clinical features of WNV may be answered.

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