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BIOLOGY, EPIDEMIOLOGY, GENETIC CHARACTERISTICS, AND RESEARCH PRIORITIES OF WEST NILE VIRUS

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ABSTRACT

West Nile fever (WNF) is an acute viral, natural foci infectious disease with a zoonotic mechanism of transmission. WNF has a high incidence in countries with a temperate climate in the summer-fall season. The causative agent is West Nile virus (WNV), which belongs to the Flavivirus genus of the Flaviviridae family. WNV was first isolated in the West Nile district of Uganda in 1937 from the blood of a native Ugandan woman. Several sporadic cases were then reported in Israel, Egypt, India, France, and South Africa from the 1950s to 1980s. However, WNV became a global public health concern after introduction of the virus in New York in 1999, which consequently led to its massive spillover across almost all of the United States, Canada, and Central America. In the 1990s, several significant outbreaks of WNF also occurred in Russia. The virus currently circulates in almost all countries of the African continent, Asia (mainly on the Hindustan subcontinent), Israel, and Europe. In Kazakhstan, WNF cases have mainly been reported in territories bordering Russia and in some areas of the Turkestan oblast. Birds serve as amplifier hosts, and mosquitoes, mainly of the genus Culex, are the primary vectors. Human and horses are the dead-end hosts of the virus. The clinical manifestations of WNV infection in humans range from asymptomatic illness to encephalitis, leading to various neurodegenerative diseases. This article reviews current data on the biology, epidemiology, ecology, geographical distribution, virology, pathology, structure, and genome characteristics of WNV, as well as the main laboratory diagnosis methods and further research priorities.

Key words: West Nile fever (WNF), West Nile virus (WNV), mosquito, Culex, Flavivirus, genotype.

INTRODUCTION

West Nile Virus (WNV) is a neurotropic human pathogen that causes West Nile fever (WNF) and encephalitis. WNF is characterized by fever, serous inflammation of the meninges (very rarely - meningoencephalitis), systemic lesions of the mucous membranes, lymphadenopathy and, less commonly, a rash. WNV is classified in the serocomplex of Japanese encephalitis of the *Flavivirus* genus, the family of *Flaviviridae* , and is one of the most significant flaviviruses worldwide. The *Flavivirus* genus of the family *Flaviviridae* consists of more than 70 viruses, most of which are arboviruses, i.e. viruses transmitted through biological transmission by susceptible vertebral blood-sucking arthropod carriers. In most cases, the transmission of infection is carried out through the bite of a carrier - a mosquito or a tick, which allows to divide flavivirus infections into those transmitted by ticks or mosquitoes [1-4].First described in 1937 during a case of febrile illness in Uganda, WNV caused infrequent outbreaks, usually associated with mild febrile illness, from the 1950s to the 1980s in Israel, Egypt, India, France and South Africa. The first outbreak of neuroinvasive disease caused by WNV was recorded among elderly people in Israel in 1957

[3-4]. Subsequent outbreaks included cases of neuroinvasive WNV disease in adults and children [5-8, 9].

Since mid-1990s, the frequency, severity, and geographic range of WNV outbreaks has increased, and outbreaks of WNM meningitis and encephalitis, affecting mostly adults, have occurred in Bucharest, Romania in 1996, Volgograd, Russia in 1999, and Israel in 2000 [10-13]. WNV crossed the Atlantic and reached the Western Hemisphere in the summer of 1999, when an accumulation of patients with encephalitis was recorded in the metropolitan area of New York State, and within 3 years the virus spread to most of the US states and neighboring countries, Canada and Mexico [8-9]. In addition, WNV was also detected in Central and South America as a result of field surveillance studies, suggesting a potential risk of an outbreak in humans [8-9, 14-16].

The first epidemic outbreak of West Nile fever in Russia was established in 1999 (in the Astrakhan, Volgograd oblasts and Krasnodar region), when 560 laboratory-confirmed cases were recorded [17-18]. In 2010, there were repeated outbreaks of WNF in the same regions with 510 cases. Over the 14-year period (from 1999 to 2013), the expansion of the WNF distribution area was established. In total 2316 cases of WNF were detected, including 1253 in the Volgograd oblast, 544 in the Astrakhan oblast, 212 in the Rostov oblast, 104 in the Krasnodar region, 103 in the Voronezh oblast, 39 in Lipetsk, 39 in Saratov, 18 in Samara, 5 in the Belgorod [10-11,17, 19]. Over the 77 years since its discovery, the virus had spread in a vast region of the globe and is currently considered as the most significant causative agent of viral encephalitis in the world.

The first laboratory-confirmed data on WNV circulation among people in Kazakhstan were obtained in 1972 in the Kyzylorda oblast. To date, studies of WNF in Kazakhstan are single, they were conducted only in the West Kazakhstan and Turkestan oblasts and are mainly aimed at studying the vectors of the WNV, screening healthy population for IgG antibodies against WNV [20-22].

Factors of relevance of problems associated with WNV are the possibility of WNV transfer by migratory birds, their ability to replicate in new species of mammals, and rapid adaptation to natural conditions, which ensures the establishment of new natural foci of West Nile fever, in which the population living in this area is also involved [1-2,8-9].

Given the expansion of the WNF distribution boundaries, the registration of large outbreaks in the border areas with Russia (Volgograd, Astrakhan, Saratov oblasts), incomplete data on the WNF in Kazakhstan, the lack of sanitary and epidemiological surveillance of this infection in Kazakhstan, the lack of virus-specific drugs, modern effective methods of treatment, and often the prevention of diseases caused by WNV, there is a need for more in-depth scientific research in this area [10-11,22].

The purpose of this review article is to present and summarize recent data on the structure of the genome, genetic characteristics, epidemiology, transmission and infection of people, virology as well as diagnostic methods. We discuss and analyze the data collected and presented over the past decade, and present future research directions.

Epidemiology, ecology and distribution of West Nile virus

West Nile Virus is an etiological agent of WNF. Invertebrates and vertebrates are reservoirs of WNV in nature, among which migratory birds are of great importance in its distribution. In the enzootic transmission cycle, WNV circulates between birds and mosquitoes of the genus *Culex* , but sometimes it can infect humans and some vertebrates and lead to death (figure 1) [1, 8-9].

WNV was repeatedly, in various areas, isolated from birds of various families and orders. Birds are of primary importance in the circulation of the West Nile virus due to their ability to develop high titers of viremia in the blood, sufficient to infect mosquitoes. Experimental studies conducted in 2003 by researchers from Omsk on the infection of birds of various orders and families allowed to identify several species that are particularly susceptible to WNV (23-24). For example, high titers of viremia develop in birds of families *Corvidae* , *Laridae* and *Charaiidae* , and then birds of family *Columbidae* , *Strigidae* and *Picidae* come with lower titers. The most important for WNV circulation in the U.S. and other countries are blue jay (*Cyanocita cristata),* common grackle (*Quiscalus quiscula*), house finch (*Carpodacus mexicanus*), American crow (*Corvus branchyrhynchos*), and house sparrow (*Passer domesticus*) [25].

In Russia (Volgograd, Astrakhan oblasts) from birds of the anthropogenic complex of great epidemiological importance as carriers of WNV are corvids and pigeons, the high number of which in settlements can lead to infection of synanthropic mosquitoes which infect humans. It should be noted that birds play the role not only of the WNV reser-

voir, but also as its carriers (vectors) over long distances during the migration season [23-24].

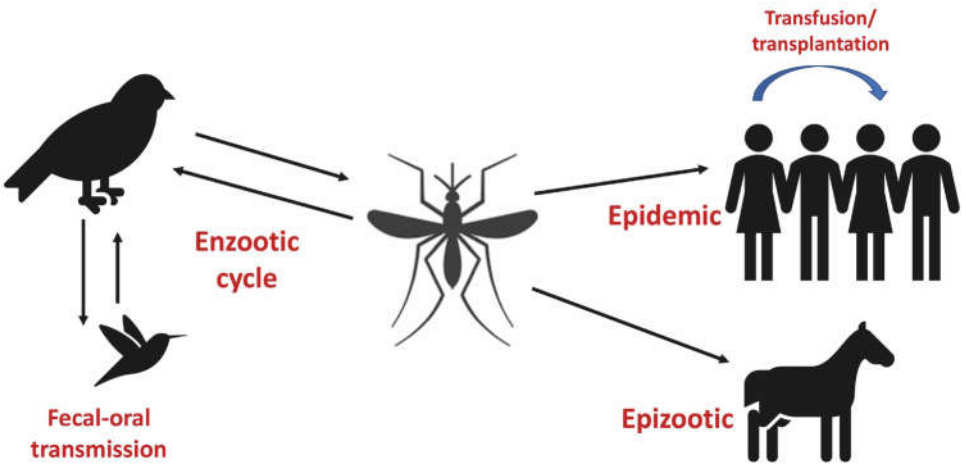

Fig. 1. Transmissive cycle of West Nile virus.

Mammals (wild and domestic animals) do not play a significant role in maintaining the circulation of WNV, since the titers of viremia developing in them are insufficient to infect mosquitoes. Among domestic animals, only horses exhibit severe clinical symptoms in the form of a fever with symptoms of meningoencephalitis and frequent death. Marsh frogs (*Rana ridibunda*), common brown lemurs (*Lemur fulvus*), hamsters, fox squirrels (*Sciurus niger),* eastern gray squirrels (*Sciurus carolinensis*), eastern cottontails (*Sylvilagus floridanus*), and eastern chipmunks (*Tamias striatus*) have been reported to develop viremia levels expected to support vector transmission [26-29].

The main vectors of the West Nile virus are blood-sucking mosquitoes, and in some cases *Argasidae* and *Ixodidae* ticks. Mosquitoes of at least 43 species of 11 genera are of primary epidemiological importance. Mostly the *Culex* genus, in rare cases mosquitoes of genera *Anopheles* and *Aedes* can be a vectors of WNV, but their role in WNV circulation needs to be better evaluated [8-9, 26, 30-32].

In various ecosystems, different mosquito species have varying significance in epidemiology and epizootology. Some species of mosquitoes feed on the blood of birds only (*C. pipiens, C. restuans*), providing the circulation of the virus in natural and anthropogenic biocenoses, others (*C. salinarius*) feed on the blood of birds, mammals (including humans) and are therefore epidemiologically significant vectors. In the largest epidemiological outbreaks of WNF worldwide, the following mosquito species played a major role as WNV vectors: in Romania in 1996 - *Culex pipiens* mosquitoes, in Eqypt, South Africa and Israel - *C. univittatus*, in France -*C. modestus* , in India and Pakistan - *C. vishnui, C. quinquefasciatus, C. fatigans*, in Russia - *C. modestus* and *C. pipiens* [8-9, 26, 30-32]. According to the literature, the mosquito fauna in Kazakhstan, within Mangystau, Atyrau, Aktobe and West Kazakhstan oblasts, is represented by 25 species. In the landscape and climatic zones of these areas, mosquitoes of four genera can be potential vectors of the WNF virus: *Anopheles* (*A. maculipennis, A. hyrcanus*), *Aedes* (*Ae. vexans*), *Ochlerotatus* (*O. caspius, O. dorsalis, O. cantans, O. detritus, O. subdiversus*) and *Culex* (*C. modestus, C. pipiens, C. pusillus*) [20].

The pathogen of West Nile fever has been repeatedly isolated from *Ixodidae* and *Argasidae* ticks, confirmed by numerous field and experimental studies. For example, this virus was isolated in Egypt from *Argas hermanii* ticks collected in winter [8].

West Nile Fever is a sporadic, natural foci disease. Anthropogenic transformation of the biosphere, epizootics among domestic or synanthropic animals, which, in turn, develop after epizootics among wild animals, climatic changes that have a complex and often ambiguous effect on the areas of the infectious diseases≥ spread and intensity of the epidemic process, are some of the main causes of the occurrence of annual epidemiological situations related to WNF. In abnormally warm years, seasons, individual months, favorable conditions are created for a sharp increase in the prevalence of vector-borne infections. Regional climate changes, especially temperature increase and precipitation, affect a diverse set of physical and biological systems of vectors that determine the epidemiological situation of WNV [8-9, 26].

WNV was first isolated in 1937 in a West Nile province in Uganda from a patient with mild fever, and thus had been known in the Old World for over 60 years before it crossed the Atlantic [3, 8-9]. For

many years after describing WNV, sporadic morbidity and small outbreaks of WNV have been reported in Africa, the Middle East and Asia [33-34]. The first significant outbreaks of WNF were recorded in 1950-1954 and in 1957 in Israel, as well as in 1974 in South Africa, with infection of about 3,000 people. No lethal cases were reported during these outbreaks. Cases of WNV-induced meningoencephalitis were first observed in 1957 during an outbreak in Israel (among elderly patients), and later in India (among children) with fatal outcomes. In 1951, WNV was also isolated in Israel from a febrile sick child [35]

Since the 1990s the nature of the pathogenicity of epidemic outbreaks of WNF has sharply changed in an unfavorable direction. In 1994, an outbreak occurred in Algeria, during which about 50 cases of the disease were recorded with 8 deaths. A subsequent outbreak of WNF was recorded in Europe, Romania in 1996, with high level of mortality (about 9%). In 1997, Israel experienced a major epizooty of WNF with acute neurological manifestations on a goose farm, which led to high mortality of birds. Among people, a WNF epidemic occurred in 2000, although as early as 1999, two fatal cases of WNF were recorded. In total, in 2000, 417 confirmed cases of WNF were registered in Israel, and half of cases were characterized by lesions of the central nervous system (encephalitis). The mortality rate was, according to various sources, from 8 to 14%. In 1999, almost simultaneously, outbreaks of WNF occurred in southern Russia and in New York, USA, with a similar mortality rate. It should be noted here that until 1999 the American continent was free of the virus. However, a year later, a focus appeared in Florida, and by 2003-2004 almost the entire territory of the USA, South Canada and Latin America became endemic with a high incidence and mortality rate for this infection. According to the Centers for Disease Control and Prevention, between 1999 and 2008 about 29 thousand people were infected and became ill, 1124 of them died in the US. The maximum incidence was noted in 2003 - 9862 confirmed cases in the USA, 24 of them were fatal, in Canada -1335 cases, of which 10 were fatal. In 2006, WNV was discovered in Argentina [1-2, 8-15, 26].

In Russia, the sporadic incidence of WNF has been recorded since the mid-1960s. In 1991-1996, when the incidence was sporadic in nature, in the Astrakhan oblast 10 cases of WNF were recorded. In 1999, about 600 cases were confirmed, and in addition to the Astrakhan oblast, for the first time, patients were also registered in the Volgograd oblast and in the Krasnodar region. Later, the incidence of WNF was recorded in 2001-2002, but on a smaller scale [9-11]. A new limited outbreak of WNF was noted in the Astrakhan oblast in 2005 (about 70 cases of the disease).

Until 1999, the area of WNV was limited to the eastern hemisphere. However, now its area covers vast territories within the equatorial, tropical and temperate (southern part) climatic zones in Africa, Europe, America, Asia, Oceania and Australia.

The trend of a gradual increase in the incidence of WNF in the European Region, which began in 2015 (130 cases), in 2017 (203 cases) led to a significant increase in the incidence [36]. According to the data of the European Center for the Prevention and Control of Diseases, in the countries of the European Region, 2056 cases of WNF with a mortality rate of 8.6% were registered in 2018, of which:

- in countries of EU there were 1499 cases, including Italy - 577 cases (45 lethal), Greece - 309 (47 lethal), Romania - 277 (42 lethal), Hungary - 214 (1 lethal), Croatia - 53, France - 25, Austria - 20, Bulgaria - 15 (2 fatal), Slovenia - 3, Cyprus - 1 case;

- in countries bordering the EU there were 577 cases of WNV infection, including in Serbia 415 (35 deaths), Israel 128, Kosovo 14 cases with 3 lethal.

On August 22ć29, 2019 EU Member States reported 52 human cases in Greece (38), Romania (7), Hungary (4), Cyprus (2) and Bulgaria (1). Additional four cases were reported in the EU neighbouring Serbia. All human cases were reported from areas that have been affected during previous transmission seasons. That week seven deaths were reported in Greece [36].

Thus, in the countries of the European region, in particular, in the countries of the south of Europe and the Mediterranean (Greece, Italy, Romania, Serbia, Israel), there has been a significant increase in the number of registered cases of WNF.

According to the U.S. Centers for Disease Control and Prevention, there has been no upward trend in the incidence of WNF in the North American continent over the past 5 years (2014 - 2205 cases, 2015 - 2175 cases, 2016 - 1938 cases, 2017- 1984cases, 2018 ć 2204 cases). In general, the incidence did not exceed the level of the epidemic situation in 2012, when 4249 cases were recorded [37]. According to the reports of the Public Health Agency of Canada over the past five years, in Canada there has been a tendency to an increase in the incidence of

WNF (2015 - 80 cases, 2016 - 104 cases, 2017 - 200, 2018 - 340) [38].

In the season of 2018 on the territory of the Russian Federation (RF), the manifestation of WNF was characterized by the intensification of epidemic processes in endemic territories and cases of WNF infection were recorded in the following regions: in Volgograd - 28 cases, Rostov - 25 cases, Astrakhan - 9 cases and the Krasnodar region - 3 cases.

Practical interest in WNV in Kazakhstan is caused by an increase in the incidence of WNF in the Caspian region of the Russian Federation, where it has been registered since 1967 and the difficult epidemic situation in the world for viral infections. West Nile virus in Kazakhstan for the first time was isolated from*Hyalomma anatolicum* ticks, which were collected from cows in the Saryagash region and from the internal organs of the blue roster bird in 1974 in the Otyrar district of the South Kazakhstan oblast. WNV is not an endemic disease on the territory of Kazakhstan, however, specific antigens in ticks and antibodies to the WNF virus have been recorded in people in different years. For example, a random serological examination of the population of border settlements of the West Kazakhstan region found that 5.4% of people (1135 blood serums samples from rural residents) have specific antibodies to the WNF virus in the blood, which confirms the circulation of the WNV in the local mosquito population [20]. According to the data for 2019, antibodies to WNV were also detected in 7 regions of the Turkestan oblast (Otyrar, Baidibek, Maktaaral, Saryagash, Sairam, Tolebi and Tulkubas regions) ć 51 positive samples from 475 serum samples. Also, over the past 4 years in Almaty (Almaty region), there has been an increase in cases of the incidence of serous meningitis (in 2014 there were 25 patients, in 2015 - 47, in 2016 - 59, for 7 months of 2017 - 52). The etiological factor of these serous meningitis has not been established [39].

Pathogenesis and clinical manifestations

The classic model for studying the pathogenesis of WNF is newborn and adult mice of several lines and other rodents. After an infected mosquito bite, WNV infects keratinocytes and Langerhans cells [2, 8-9] which migrate to lymph nodes resulting in a primary viremia. Then the virus disseminates to kidney and spleen where a new replication stage occurs, in epithelium cells and macrophages respectively [2, 9, 26]. Depending on the level of viremia, the peak of which comes at day 3 post inoculation in mice, the virus may cross the blood-brain barrier (BBB) and enter the central nervous system (CNS), causing meningo-encephalitis. WNV infects neurons in various parts of the CNS causing loss of structure, degeneration and cell death. West Nile virus, like other flaviviruses, is cytolytic and causes apoptosis in many cells, including neurons. Several *in vitro* studies have shown that the expression of individual viral proteins - capsid or NS3 - also causes Casp9-dependent apoptosis. [40].

Flaviviruses (WNV, Japanese encephalitis virus, Dengue virus, etc.) disrupt the cellular mechanism of induction of IFN-dependent genes by acting on the activation of signaling transcription factors STAT [2, 26]. Non-structural proteins of flaviviruses NS2A, NS2B, NS3, NS4A, NS4B and NS5 act as antagonists of IFN signals. These viral proteins interact with the tyrosine kinases Jak1 and Tyk2, preventing their phosphorylation. The block of activity of the IFN action system caused by flaviviruses at the stage of signal transmission to antiviral cell genes provides the necessary conditions for viral reproduction [1-2, 8-9, 26].

WNV is able to successfully infect a wide variety of animal cell lines, including mammalian, bird, and insect cells, which is apparently ensured by the ability of the virus to bind to many highly conserved cell receptors. Such relatively wide tropism, apparently, contributes to a wide range of clinical manifestations of WNF.

Infection of WNV in people occurs mainly through bites of mosquitoes of various species, although cases of infection during blood transfusion, breast-feeding, organ transplantation, etc. are also described. Human infection with WNV can have various manifestations - from asymptomatic infection or mild fever to the development of severe forms of encephalitis and meningoencephalitis with a mortality rate of up to 12-14%. Most human infections with WNV (~80%) are asymptomatic, and symptomatic infections may vary from flu-like malaise to serious neuroinvasive diseases, for which there is no specific treatment. Less than 1% of human infections progress to severe disease, for which the most frequently reported risk factors include age, immune suppression, and chronic medical conditions including but not limited to hypertension, diabetes, and chronic renal failure [8]. WNF disease starts acutely with an increase in temperature to 38ć40°C, develops a general intoxication syndrome, which manifests itself as severe headache, nausea,

vomiting, myalgia, arthralgia, weakness and gastrointestinal symptoms. For this period, pain in the eyeballs is characteristic, scleritis and conjunctivitis are often observed. In some cases, a rash and hepato - splenomegaly are noted. The rash is predominantly seen in younger patients. Among lesions of the nervous system, benign serous meningitis is more often observed, less often - encephalitis. West Nile fever manifests itself in the following forms: febrile form meningial form, and meningoencephalitis [2, 9].

WNF virus structure and genome organization

Like most flaviviruses, the WNV represents a virion of spherical shape 50 nm in size. It has a distinct nucleocapsid, which is located in the center of the virus (about 30 nm in size) - this is a complex of protein C (capsid proteins) with nucleic acid. A membrane protein M (membrane) and surface protein E (envelope) are interspersed in the lipid membrane. The exodomains of envelop (E) protein dimers lie close to the outer surface of the virion membrane and are positioned head-to-tail. The membrane (M) protein contains two membrane spanning domains and a short ectodomain [9, 26, 41-42]. The E proteins encoded by most strains of WNV are glycosylated at a single N-linked glycosylation site (residue 154).

The genome of this virus is a ribonucleic acid with a length of approximately 11 thousand bases. This ribonucleic acid is also messenger RNA, i.e. +RNA, and it synthesizes a long polypeptide chain with a length of about 1000 amino acids. There are about 100 non-coding nucleotides at the 5≥ end of this genomic RNA, and 400 to 700 at the 3≥ end. The 5≥-end of the WNF virus genome contains the so-called flcapffi, or methylated nucleotide, and there is only a small polyA sequence at the polyA-end. The 3≥ and 5≥ end of the genome fold into RNA secondary structures that are conserved among different flaviviruses even though the majority of the nucleotides composing these structures are not conserved. Proteins C dimers and RNA binding domains are located at the C- and N-ends and separated by a hydrophobic region. The bi layered lipid envelope of the virion contains 180 molecules of E and prM/M proteins organized into prM-E heterodimers. The transition from immature to mature forms of the virion is characterized by the structural change, rotation and rearrangement of the prM-E heterodimers [41-42]

The viral genome encodes three structural proteins (C, prM/M and E) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5) (figure 2).

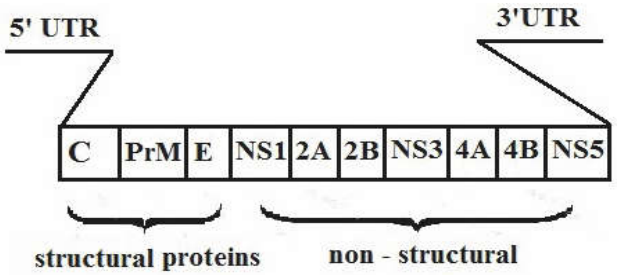

Fig. 2. WNV genome organization: the viral genome is represented with one ORF encoding 3 structural and 7 non-structural proteins.

The viral nonstructural proteins are responsible for regulating viral mechanisms of transcription, translation and replication and attenuate host antiviral responses. Protein NS1 functions as a co-factor for viral RNA replication, and this protein is the only protein secreted in blood serum of infected patients. Protein NS2A is associated with RNA replication and-suppression of IFN-beta transcription. NS3 protein has protease and helicase functions and in combination with NS2B protein has an important role in post-translational cleavage of the viral polyprotein, releasing the structural and non-structural viral proteins required for replication of virus and virion assembly. NS5 acts as a major enzymatic component of the viral replication. The NS4A functional role has not been sufficiently investigated, although evidence suggests that this protein functions as an florganizerffi of flaviviruses replication complex [2, 9, 41-42].

WNV has the ability to replicate in various cell cultures of mammalian, avian, amphibian and insect tissues. Flaviviruses enter the cell by endocytosis mediated by the receptor interaction of the host cell membrane protein with the viral envelope protein (due to co-receptors such as DC-SIGN and DC-SIGN-R, DIII RGD/RGE, Rab5GTPase and Laminin Binding Protein and others). Inside the endosome, under the influence of the interaction of receptors and/or acidic pH, the process of conformational change of the viral envelope glycoprotein E starts, as a result of which the fusion peptide, previously located inside the protein, is brought out and inserted into the lipid membrane of the endosomal vesicle. After this, the fusion of the viral and endosomal membranes occurs, as a result of which the viral nucleocapsid opens and relocates in the cytoplasm of the host cell. It is assumed that fusion peptide plays a key role in the process of fusion of membranes, while it is possible that there are other factors that ensure the interaction of lipid bilayers [41-44].

Replication, or reproduction, of the WNV- occurs in the cytoplasm of cells, and the assembly takes place in the endoplasmic reticulum, from which the

virus then secretes from the cell by exocytosis. Genome translation leads to the formation of a predecessor-polyprotein (3400 amino acids), from which, due to co-and post-translational cleavage by cellular and viral proteases, individual viral proteins (structural and non-structural) are formed. Structural proteins are further responsible for the formation and assembly of the virion, and non-structural proteins are responsible for the replication of the viral genome. Replication of the viral genome is carried out during the processing of non-structural proteins and carried out in two stages. At the first stage, a negative RNA chain that is complementary to the original + RNA of the viral genome is formed. This negative chain is preserved and used as a matrix for the production of new +RNA chains. RNA synthesis is carried out by a replicative complex, which consists of viral and cellular proteins. The main role in this complex is played by the NS5 protein. The mechanism of viral RNA synthesis has not been studied in detail yet. However, it is known that a significant role in this process is played by the interaction of some conservative structural elements of viral RNA located at the 5≥ and 3≥ ends. The formation of mature structural viral proteins and the assembly of the virion occur in several stages, with the formation of intermediate protein complexes and immature viral particles. After maturation, the virions flbud offffi from the cell, being released into the extracellular medium by exocytosis. It is also important to mention that, according to some studies, the mixture of fully mature and immature virions can initiate infection [1-2, 41-44].

Phylogenetic classification and genotypes of WNV

West Nile Virus is a member of the Flaviviridae family of single-stranded RNA viruses with linear non-segmented genomes. More than 58 members belong to the Flaviviridae family, whose name comes from the word flflaviffi, Latin for flyellowffi, because one of the most famous flaviviruses is the Yellow Fever Virus. This family currently consists of 3 genus: the first genus is *Flavivirus*, the second genus is *Pestivirus*, and the third genus is *Hepacivirus* . Pestivirus genus consists of 4 viral species that cause important animal diseases: Bovine Viral Diarrhea Virus type 1 and 2, Border Disease Virus and Classical Swine Fever Virus. The only member of the Hepacivirus genus is Hepatitis C virus. The Flavivirus genus is the largest with at least 53 species divided into 12 serologically related groups. Nowadays 4 serocomplexes are the most common and significant in the world: tick-borne encephalitis serocomplex (4 species: POW ć Powassan virus, LGT ć Langat virus, LI ć Louping ill virus, TBEV ć tick-borne encephalitis virus); Yellow fever virus serocomplex, which is represented by one branch, this is due to the fact that the virus is not very variable, and all its varieties fit into this one branch; 5-branch Japanese encephalitis serocomplex (West Nile fever virus, Kanjin virus, Murray Valley encephalitis virus, Japanese encephalitis itself and St. Louis encephalitis virus); and the last Dengue fever virus serocomplex (4 varieties of Dengue virus 1, 2, 3 and 4).

Of these, the Japanese Encephalitis Virus (JEV) group (8 species) is the one with the most human-associated disease viruses; Japanese Encephalitis Virus, St. Louis Encephalitis Virus, Murray Valley encephalitis Virus and West Nile Virus are four members of the JEV group that have been associated with widespread human and animal disease outbreaks (figure 3) [1, 9, 41].

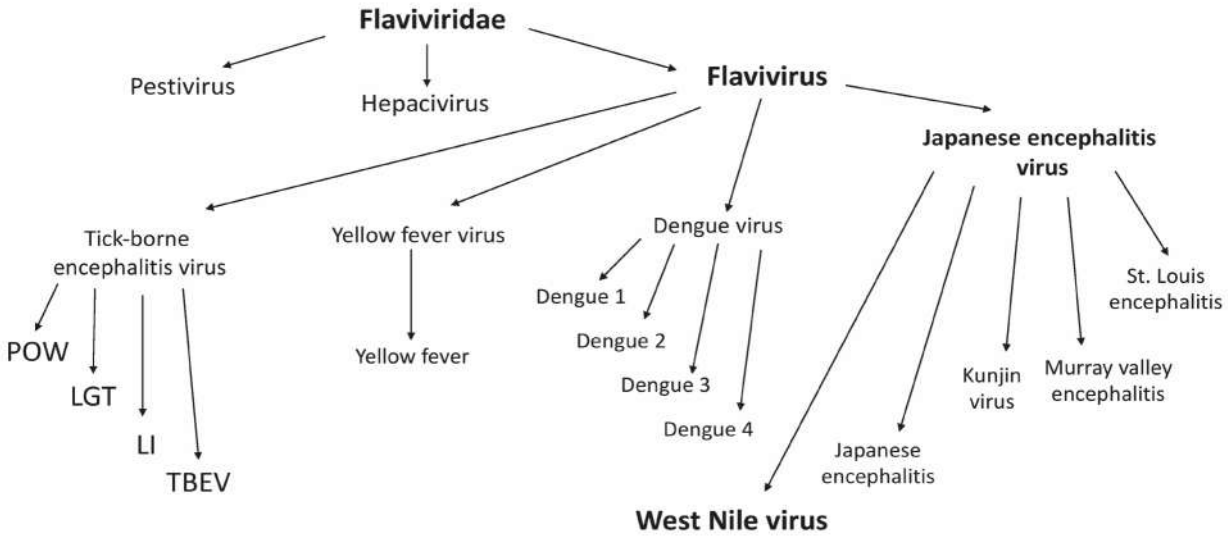

Fig. 3. WNF virus phylogenetic classification

Based on phylogenetic classification, WNV strains are divided into seven major genetic lineages [46]. Human diseases have been associated with lineages 1 and 2. Lineage 1 is the most widespread, containing isolates found in Europe, North America, Asia, Africa and Australia. This linage is further sub-classified into 1a, 1b and 1c. 1a is found mainly in Africa, Europe, North America (NY99 strain) and Asia and is further divided in six evolution clusters [46]. 1-b contains the Australian Kunjin virus. A third clade 1c which contains Indian isolates (one from a bat and other from a human) is now classified as Lineage 5. Lineage 2 strains are mainly distributed in Sub-Saharan Africa and Madagascar, but in the last decade they have been found in Europe (Hungary, Italy and Greece) and Russia. Lineage 3, also known as Rabensburg virus, contains a strain circulating in certain *Culex* and *Aedes* mosquito species in southern Moravia, Czech Republic, Austria, not known to be pathogenic to mammals. Lineage 4 is represented by a strain isolated from *Dermacentor marginatus* ticks from Caucasus [48]. Lineage 6 contains Sarawak Kunjin virus and isolates from *C. pipiens* mosquitoes in southern Spain, while lineage 7 consists of the African Koutango virus (Senegal). The lineages 4, 6 and 7 and their pathogenesis in mammals (human) are questionable and require further deep studies.

Quantitative evaluations of the nucleotide divergence between the listed genotypes of the WNV varies within 20-25%, and within individual genotypes - 5-15%. In general, a particular genetic line correlates with the geographical distribution of the virus. For example, cluster 1b contains only isolates from Australia, strains from South Africa and Madagascar belong to the second genotype, and all isolates from India are combined in the fifth genotype. However, a complete correlation between genotypes and their geographical distribution is not observed, and this is apparently due to the fact that birds that carry the virus over long distances (to other continents) play an important role in the circulation of WNV. An example is cluster 1a containing isolates of the most diverse geographical origin (Africa, Europe, North America and the Middle East) and genotype 2, which includes isolates from Sub-Saharan Africa, Madagascar, Hungary, Russia, Italy and Greece.

On the territory of the Russian Federation, the circulation of mainly three WNV genotypes was recorded - 1, 2, and 4. Moreover, according to complex molecular genetic studies, genotype 1is the dominating one.

Laboratory methods for diagnosis of WNV infection

Diagnostics of West Nile virus can be carried out using a number of different tests: enzyme-linked immunosorbent assay (ELISA) using immobilized IgG antibodies, neutralization analysis, virus detection by reverse transcription polymerase chain reaction, cell isolation by cell culture, etc. [1-2, 8-9, 26].

Laboratory diagnosis of WNV is in most cases serological, ELISA assay is performed for the detection of IgM and IgG antibodies against WNV in serum and CSF samples. At the same time, caution is advised for ELISA diagnosis because of the high degree of cross-reactivity among flaviviruses, and it is recommended to perform neutralization or other serological tests for confident determination of etiology of disease. Other serological assays include immunofluorescent antibody assay (IFA), microsphere immunoassay (MIA) and confirmatory plaque reduction neutralization test (PRNT).

The detection of WNV can also be performed using PCR methods. WNV RNA may be detected for an average of up to four days before the detection of IgM antibodies. WNV RNA is difficult to detect in serum, plasma or cerebrospinal fluid due to the low or absent viremia and, thus, it was recently demonstrated that WNV RNA can be detected in urine samples at higher load for a long period of time compared to plasma and cerebrospinal fluid [49-50].

There are several commercial PCR kits available now: Roche diagnostics (Manheim, Germany) and a transcription mediated amplification test from Novartis Diagnostics (Siena, Italy). Other PCR kits such as TaqMan based on RT-PCR have been shown to be more sensitive. Russian analogue of RT-PCR kit is AmpliSens WNF-L PCR test kit (Russia). Due to the fact that newly emerging WNV strains may have mutations, genome-wide multiple primer based real-time PCR quantitative assays were developed. For instance, in their studies Parida et al. have presented new real time loop mediated isothermal amplification (RT-LAMP) which has 10-fold higher sensitivity.

Other RT-PCR assays include newly developed molecular assays designed to detect all known lineages of WNV. For example, the assay developed by Vazquez et al. in 2016 for the detection of all known WNV lineages and real-time PCR assay for detection and genotyping of WNV lineages circulating in Africa [49-50].

The WNV can be demonstrated by using cell cultures, but these studies require biosafety level-3

(BSL-3) laboratory conditions and cell lines such as rabbit kidney (RK-13), pig kidney cells, mosquito cell lines or African green monkey kidney.

Other tests used for the diagnosis of WNV include hemagglutination inhibition test, immunoblot (western blot), microsphere immunobased assay (microfluidic system) and WNV lateral flow assays [26].

CONCLUSION

WNV is a re-emerging flavivirus, circulating worldwide between birds and mosquitoes, which impacts human and animal health. Since the middle of 1990s there were several significant outbreaks of WNV in Europe, America and Russia and now WNV is gaining public health importance.

Due to its geographic location and certain climate conditions, Kazakhstan may be on the verge of spreading WNV mainly from Russia - Kazakhstan≥s largest neighbor. Unpredictable situation of the West Nile virus risk in Kazakhstan is strongly linked to the knowledge gaps. Our knowledge on how, when and from where WN virus is entering into Kazakhstan is limited today. It is important to tackle questions on WNV ecology, main vectors and WNV strains circulating currently in Kazakhstan. Major factors which lead to WNV amplification and its distribution on the territory of Kazakhstan are also unknown. Another important knowledge gap is the impact that other co-circulating flaviviruses (and perhaps arboviruses) may have on WNV epidemiology in Kazakhstan. There are also knowledge gaps in laboratory-based diagnosis methods of WNV. The challenges with diagnostics methods are associated with WNV diversity, its ability to acquire mutations and short time to detect WNV RNA. Characterization of virus strain, in particular, virulence studies and identification of virulence determinants demand proper experimental animal models. Although interactions between many cellular proteins and virus components have been identified, the functions of most of these interactions have not been delineated yet and also require further studies.

Currently, the lack of comprehensive epidemiological data on WNV circulation in Kazakhstan, effective diagnostic methods, virus-specific drugs, effective treatment methods, and often the prevention of diseases caused by WNV, explains the scientific interest in this problem. It is necessary to intensify research efforts for WNV studies and maintain existing research capacities in Kazakhstan. This may help in the design and implementation of more efficient and cost-effective control strategies since introduction of WN virus is an ongoing risk and reality.

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БАТЫС НИЛ БЕЗГЕГІНІҢ ВИРУСЫ: БИОЛОГИЯСЫ, ЭПИДЕМИОЛОГИЯСЫ, МОЛЕКУЛАЛЫҚ-ГЕНЕТИКАЛЫҚ СИПАТТАМАСЫ ЖӘНЕ ЗЕРТТЕУ БАСЫМДЫҚТАРЫ

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ТҮЙІН

Батыс Нил безгегі (БНБ) - бұл жедел вирустық, табиғи-ошақтық, трансмиссиялық таралу механизмі бар, жазда және күзде қоңыржай аймақтарда тіркелетін инфекциялық ауру. Бұл ауру қоздырғышы – Батыс Нил безгегінің вирусы (БНБВ)*Flaviviridae* тұқымының *Flavivirus* тұқымдасына жатады. БНБВ алғаш рет 1937 жылы Угандада (Батыс Нил округі) Уганда тумасының қанынан бөлінген. 1990-шы жылдарға дейін осы вирус 1950-1980 жылдар аралығында Израильде, Египетте, Үндістанда, Францияда және Оңтүстік Африкада бірнеше рет кездескен. Бұл вирус Америка Құрама Штаттарына, Нью-Йорк қаласында 1999 жылы шыққанынан бастап АҚШ-тың барлық дерлік штаттарында, Канада және Орталық Америкада жаппай таралуына әкелді және денсаулық сақтаудың жаһандық проблемасына айналды. 1990-жылдары Ресейде де бірқатар маңызды Батыс Нил безгегінің тарауы тіркелген. Вирус Африка континентінің барлық дерлік елдерінде, Азияда, негізінен Үндістанның субконтинентінде, Израильде және Еуропада таралаған. Қазақстанда БНБВ Ресеймен шекаралас аймақтарда және Түркістан облысының кейбір аудандарында тіркелген. Құстар БНБВ негізгі резервуарлары және*Culex* тұқымының масалары негізгі тасымалдаушылары болып саналады. Адам мен жылқылар – соңғы тасымалдаушылары. Батыс Ніл инфекциясының адамдардағы клиникалық көріністері асимптоматикалық аурудан. энцефалитке дейін, әртүрлі нейродегенеративті ауруларға әкеледі. Бұл мақалада Батыс Нил безгегінің вирусының биологиясы, эпидемиологиясы, географиялық таралуы, вирусология, атология, вирустың құрылымы мен геномы туралы соңғы мәліметтер, сондай-ақ зертханалық диагностика әдістері және одан әрі зерттеу бағыттары қарастырылған.

Негізгі сөздер: Батыс Нил безгегі (БНБ), Батыс Нил безгегінің вирусы (БНБВ), маса*Culex, Flavivirus,* генотип.

ВИРУС ЛИХОРАДКИ ЗАПАДНОГО НИЛА: БИОЛОГИЯ, ЭПИДЕМИОЛОГИЯ, МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКАЯ ХАРАКТЕРИСТИКА И ПРИОРИТЕТЫ ИССЛЕДОВАНИЙ

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АБСТРАКТ

Лихорадка Западного Нила (ЛЗН) - это острое вирусное, природно-очаговое инфекционное заболевание с трансмиссивным механизмом передачи, зарегистрированное в странах с умеренным климатом в летний и осенний период. Возбудителем является вирус Западного Нила (ВЗН), который принадлежит к роду *Flavivirus* семейства *Flaviviridae*. ВЗН был впервые выделен в Уганде (округ Западный Нил) в 1937 году из крови коренной жительницы Уганды. До 1990-х годов этот вирус имел несколько спорадических случаев в Израиле, Египте, Индии, Франции и Южной Африке с 1950-х по 1980-е годы. Данный вирус стал глобальной проблемой общественного здравоохранения после возникновения вируса в США, Нью-Йорк, в 1999 году, что привело к его массовому распространению на территории почти всех штатов США, Канады и Центральной Америки. В 1990-х годах в России также произошло несколько значительных вспышек. Вирус циркулирует почти во всех странах Африканского континента, в Азии, главным образом на субконтиненте Индостан, в Израиле и в Европе. В Казахстане ВЗН зарегистрирован на территориях, граничащих с Россией, и в некоторых районах Туркестанской области. Птицы являются основными резервуарами, а комары, в основном рода *Culex,* переносчиками ВЗН. Человек и лошади – конечные носители. Клинические проявления инфекции Западного Нила у людей варьируются от бессимптомного заболевания до энцефалита, приводящего к различным нейродегенеративным заболеваниям. В этой статье рассмотрены и проанализированы последние данные о биологии, эпидемиологии, экологии, географическом распределении, вирусологии, патологии, структуре и геноме ВЗН, а также методов лабораторной диагностики и дальнейшие приоритеты исследований.

Ключевые слова: лихорадка Западного Нила (ЛЗН), вирус Западного Нила (ВЗН), комар, *Culex, Flavivirus,* генотип.