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ELIMINATION OF THE EPIDEMIC OF VILYUISK ENCEPHALOMYELITIS

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The article presents data on the termination of the epidemic of Viliuisk encephalomyelitis (VEM) in the Republic of Sakha (Yakutia), Russian Federation. VEM is a fatal chronic central nervous system disease that has claimed hundreds of lives. Originally found only in a small population living in the Viliuisk ulus (a Siberian administrative district), VEM later spread to densely populated areas of Central Yakutia. The occurrence of secondary cases among previously unaffected populations indicates that VEM was a transmissible disease with a mode of transmission characteristic of other chronic infections.

Decrease in close contacts between patients during acute and subacute phases of VEM with the surrounding population through prolonged hospitalization of patients in specialized medical institutions and improved social and hygienic living conditions in Yakut villages was followed by a slow decline in new cases of VEM; incidence slowly decreased in the 1980s and 1990s, reaching zero in the 2010s. No new cases of VEM have been reported since 2012. The elimination of the VEM epidemic prevented the disease from spreading into unaffected areas of Yakutia and other parts of the Russian Federation and might well have kept it from introducing to the world yet another emerging infection.

Keywords: Viliuisk encephalomyelitis, territorial distribution, disease prevention, Eastern Siberia, Republic of Sakha (Yakutia).

Introduction. VEM was first observed about 170 years ago in several villages around *Lake Mastakh* of the Viliuisk ulus (a Siberian administrative district) [4]. Its presence in the area was later confirmed by a medical team [3]. Most likely, the disease had smoldered for centuries in small nomadic Siberian tribes. In the 1930s, the population of such tribes was forcibly relocated to larger Yakut villages on the other side of Viliui River in order to organize collective farms. Doctors began to notice that a fatal neurological disease was occurring among the new settlers. Contacts with VEM patients expanded in the villages and farms, and, by the 1950s, the number of new cases had skyrocketed. In the 1960s, VEM spread to neighboring areas along the Viliui River, and then to densely populated industrial areas of Central Yakutia, resulting in an epidemic that was difficult to control [18]. The greatest spread of VEM occurred during the period of intense and well-documented migration of people after the end of the Second World War.

Systematic studies to understand the nature of the VEM epidemic and prevent its further spread were undertaken in the 1950s by Prokopiy Andreevich Petrov [7, 8], who would turn 100 this year. P.A. Petrov's research was supported and continued by other investigators in the following decades [6, 10, 15]. As part of these studies, an unusual virus, termed *Viliuisk virus,* was isolated from patients [9]. Viliuisk virus cross-reacts with *Theiler's murine encephalomyelitis virus* (TMEV) in serologic tests [12], however, the nucleotide sequences of the Viliuisk virus differ from the classical representatives of TMEV, therefore the Viliuisk virus was renamed the *Viliuisk human encephalomyelitis virus (VHEV)* and recognized as a separate Theilovirus clade, the first of a new group of *human TMEV* viruses within the *Theiler's virus* group [15]. The etiologic relationship between VHEV and VEM has never been established [13].

The ***objective of this study*** was to analyze long-term epidemiological data on the incidence and territorial distribution of VEM and to evaluate the hypothesis that the elimination of the VEM epidemic resulted from preventing close contacts between patients in the acute and subacute phases of VEM and the surrounding population. Opportunities for close contacts were reduced by introduction of prolonged hospitalization of VEM patients in specialized medical institutions as well as by general improvement of social and hygienic living conditions in Yakut villages.

Materials and methods. Systematic documentation and registration of VEM cases began in 1951. Particular attention was paid to the early identification of patients with suspected VEM. Complaints of high fever and headache by a resident of an endemic village were sufficient reason to consult a neurologist, and patients with neurological symptoms were sent to one of two specialized hospitals: the *Neurological Department of the Viliuisk Regional Hospital* (later the *Viliuisk Psychoneurological Hospital*) or the *Department of Encephalitis of the Yakutsk Republican Hospital* (until 1998). Expeditions of neurologists and epidemiologists from Yakutsk and Moscow periodically visited each settlement in the endemic zone to identify new patients. In 1992, a new State Program "*Biology of Viliuisk Encephalomyelitis*" was adopted; it was later closed, but, by order of the Ministry of Health of the Sakha (Yakut) Republic since 2000, all neurologists in the ulus are required to submit reports on monitoring of patients with chronic VEM. All patients with suspected VEM still undergo inpatient examination in the *Neurological Department of the Republican Hospital No. 2, Emergency Medical Aid Center* (directed by Dr. L.T. Okoneshnikova). Diagnosis of VEM is based on clinical examination and investigations, including testing of the cerebrospinal fluid, computed tomography or magnetic resonance imaging of the brain, and postmortem pathological examination.

Clinical variants. *Acute VEM* is characterized by prolonged fever (up to several months), meningeal signs, lymphocytic pleocytosis in the cerebrospinal fluid (CSF), and persistent neurological signs, including ophthalmoparesis, spastic tetraparesis and, in some cases, generalized tonic-clonic seizures. *Subacute VEM* develops in patients who have survived the acute phase of the disease. It

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is a slowly progressive neurological syndrome with dementia, dysphagia, dysarthria, spastic tetraparesis or paraparesis of the lower extremities, bradykinesia, postural instability and muscle stiffness. CSF pleocytosis with increased total protein concentration persists for months or years. Magnetic resonance imaging (MRI) shows signs of significant brain atrophy [5]. Patients usually die within one to six years as disease progresses.

In some patients, the disease stopped progressing at some point during the subacute phase; in others the chronic disease began gradually, without a recognized acute onset. Some such patients lived with chronic VEM for the next 20, 30, or even 40 years in a state of profound disability with cognitive impairment and difficulty speaking and walking. The VEM patient's appearance and behavior took on characteristic features: abnormal behavior with inappropriate laughter or tears, a hunched posture, slow movements. Residents of the affected villages call this condition "*bokhoror*" meaning "stiffness" in the Sakha language. Patients with chronic VEM eventually die, most often from trauma, pneumonia, or kidney failure.

The ratio between acute, subacute and chronic forms VEM changed during the epidemic; acute-onset cases predominated in the 1950s and 1960s [7, 8, 11]; in the 1970s, there were about the same numbers of cases with acute and insidious onsets of the disease. By the 1980s and 1990s, 80% of cases had insidious onset, developing directly into a chronic form of VEM [6].

In the CSF of patients with subacute and chronic VEM, oligoclonal immunoglobulins were detected by isoelectric focusing and subsequent immunoblotting with antibodies against human *IgG*, a technique used as a useful diagnostic test to differentiate VEM from non-inflammatory syndromes. Detection of *IgG* bands had a diagnostic sensitivity of 93% with a specificity of 80% [14]. Oligoclonal *IgG* bands persisted in CSF up to three decades after the onset of the disease.

Postmortem studies of VEM patients showed multiple micronecrotic lesions surrounded by T- and B-lymphocytes and reactive astrocytes in brains. Such lesions were present in the cerebral cortex, basal ganglia, cerebellum and brainstem; massive loss of neurons (by lysis) and dystrophic changes in the preserved nerve cells were found inside and outside the necrotic foci [17]. Small blood vessels are surrounded by inflammatory cuffs consisting of activated T-lymphocytes, natural killer cells, and killer-like cytotoxic T-lymphocytes [1]. With the transition to a chronic course, fibrous meninges and adhesions appeared, impeding the circulation of cerebrospinal fluid and leading to hydrocephalus and cerebral atrophy. Acute, subacute, and chronic VEM were clearly phases of the same underlying disease with differences corresponding to the rate of progression. Inflammatory changes or their consequences can be observed at each phase.

Thus, we have developed strict criteria for the diagnosis of VEM, excluded diseases of a different nature, and created an electronic database containing 356 cases that met the diagnostic criteria for definite VEM.

Statistical analysis. The average incidence rates of VEM were determined based on the number of new cases recognized within each decade: 1940-49, 1950-59, 1960-69, and so on. The population size was estimated by interpolating the census data of the Republic of Sakha (Yakutia) for 1949, 1954, 1959, 1970, 1979, 1989, 2002 and 2010. The territorial distribution of VEM was determined using Google Earth (http://earth.google.com/) by measuring the distance between the patient's place of residence and the epicenter (*Lake Mastakh* in the Viliuisk ulus). Student's t-test was used to determine the significance of differences between observed estimates of epidemiological parameters.

Results and discussion. During the course of this long-term study, we found that patients with definite VEM were almost all ethnic Sakha (Yakut), with the exception of six Evenk and eleven patients born of Sakha-Evenk marriages. All patients came from small villages. The ages at disease onset ranged from 11 to 68 years. The average age at disease onset increased from 30.2 (CI 27.5–33.0) years at the beginning of the epidemic to 37.1 (CI 35.1–39.1) years at the peak of the epidemic and remained at this level. The ratio of affected women to men changed from 2:1 in the 1950s and 1960s to about 1:1 in the following decades. The average incidence of VEM in the Viliuisk ulus reached the level of 286-840 cases per 100 thousand population per decade in 1940–1980. In other regions of the Republic of Sakha (Yakutia) taken together it was 14 to 37 per 100 thousand per decade. The peak incidence of VEM in the Viliuisk ulus occurred in 1954, while in other regions of the Republic it peaked in 1976 ($p < 0.05$). In the 1980s, VEM incidence began to decline first, and somewhat faster, in the other regions of the Republic of Sakha (Yakutia), followed later by a decline in the original endemic villages of Viliuisk ulus (Fig. 1). The decline continued into the 1990s and the 2000s.

Since 2012, no new cases of VEM have been reported in any part of the Republic. As of January 2020, only 24 patients from the VEM database remained alive, all in advanced stages of chronic VEM.

Trends in territorial spread. The total number of villages affected by VEM increased from four in the 1940s to 18 in the 1950s and 52 in the 1970s. During that time, the area of VEM distribution increased 15 times. After the discovery of very rich deposits of coal, metals, oil and natural gas in other parts of the Republic, people began to move from Viliui villages, further impoverished during the war, to industrial townships in Central Yakutia. VEM then appeared among local residents of Central Yakutia, most of whom had never been to Viliui. By the 1970s, people throughout almost the entire territory of Central Yakutia were affected (Fig. 2).

The circles delineate areas of concentration of 90% of new cases; the blue dots in the centers of the circles represent the geographic centers.

Mechanisms of transmission. P.A. Petrov in early studies [7] noted that in some affected families there were as many as five patients with VEM. We investigated this phenomenon. Complete family histories were obtained for 194 families of which 27 had more than one VEM case, two per family in 24 and three per family in three. Multiple cases of VEM in the same household were observed more often than expected based on random distribution for both genetically related family members ($p < 0.0001$), and adopted family members ($p < 0.001$). The median incubation time between the onset of disease in the original case and that in the secondary case was 14.1 years for genetically related and 4.6 years for adopted family members [13].

The sequence of events in these families supports the view that VEM was transmitted through prolonged intra-household contact with a patient manifesting the disease, sometimes passing to unrelated persons in non-endemic regions. However, the exact transmission mechanisms remain undetermined.

Prevention of further spread. Reliable records of hospitalization were available for 180 patients with diagnoses of definite VEM from 1965-1980. Of these, 66 patients were first hospitalized in the acute phase of the disease. Patients remained in the hospital during the entire period of the acute phase, showing manifestations of illness such as low-grade

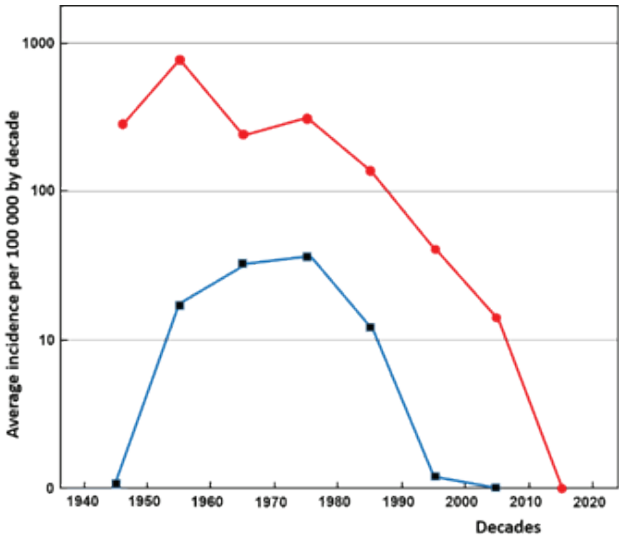

Fig. 1. The incidence of Viliuisk encephalomyelitis by decade as cases per 100 thousand inhabitants of the Viliuisk ulus (red curve) and other regions of the Republic of Sakha (Yakutia) combined (blue curve)

fever of 37.1-38°C and pleocytosis in the CSF exceeding 30 cells per 1 mm^3, evidence for an ongoing inflammatory process. The duration of the first hospitalization of patients in the acute phase of illness varied from 17 to 518 days, on average 114 days, comprising 80 to 100% of the total duration of the acute phase (Fig. 3, left panel).

Patients with *subacute VEM* repeatedly returned to the encephalitis ward to confirm the diagnosis, determine the rate of disease progression, adjust the treatment, and confirm disability. The total times patients with subacute VEM spent in hospitals ranged from 19 to 2074 days, on average 288 days, comprising 20% of the average total duration of the disease (Fig. 3, middle panel). In addition, many patients with subacute VEM, on average about 40% of them, depending on family circumstances, ended up in the Sosnovka Nursing Home (a selected special long-term care facility in the village of Sosnovka), Viliuisk ulus. Thus, patients with subacute VEM were in either a hospital or a skilled nursing home for an average of about 60% of the total duration of the disease.

Of the patients with *chronic VEM*, disabled people who had no other means of subsistence, more than 60% of the total time of their illness were kept in hospitals or remained in the Sosnovka Nursing Home (Fig. 3, right panel). Prolonged hospitalization and nursing home care helped avoid or postpone appearance of complications such as pneumonia or kidney failure, while keeping patients away from close contact with susceptible family members and neighbors.

Patients with subacute and chronic VEM who stayed with their families either temporarily or permanently were eligible for the highest level of disability insurance and were not required to work. A law passed in the mid-1960s limited contacts between patients and fellow villagers during summer fieldwork, when workers lived together in overcrowded agricultural camps away from home. In the 1980-1990s, life in Yakut villages became more comfortable; most residents began to build standard wooden houses. Improved living conditions led to fewer close contacts between VEM patients and vulnerable family and community members.

We conducted a retrospective socio-economic study of families in regions with a high incidence of VEM [2, 16]. Using a standard prepared questionnaire, we interviewed 30 patients with definite chronic VEM, 69 members of their families who were in long-term contact with patients, and 39 people living in the same settlements but not in physical contact with patients (control group). Patients with VEM were raised in families with an average of six children. Close relatives (grandparents, uncles and aunts) lived

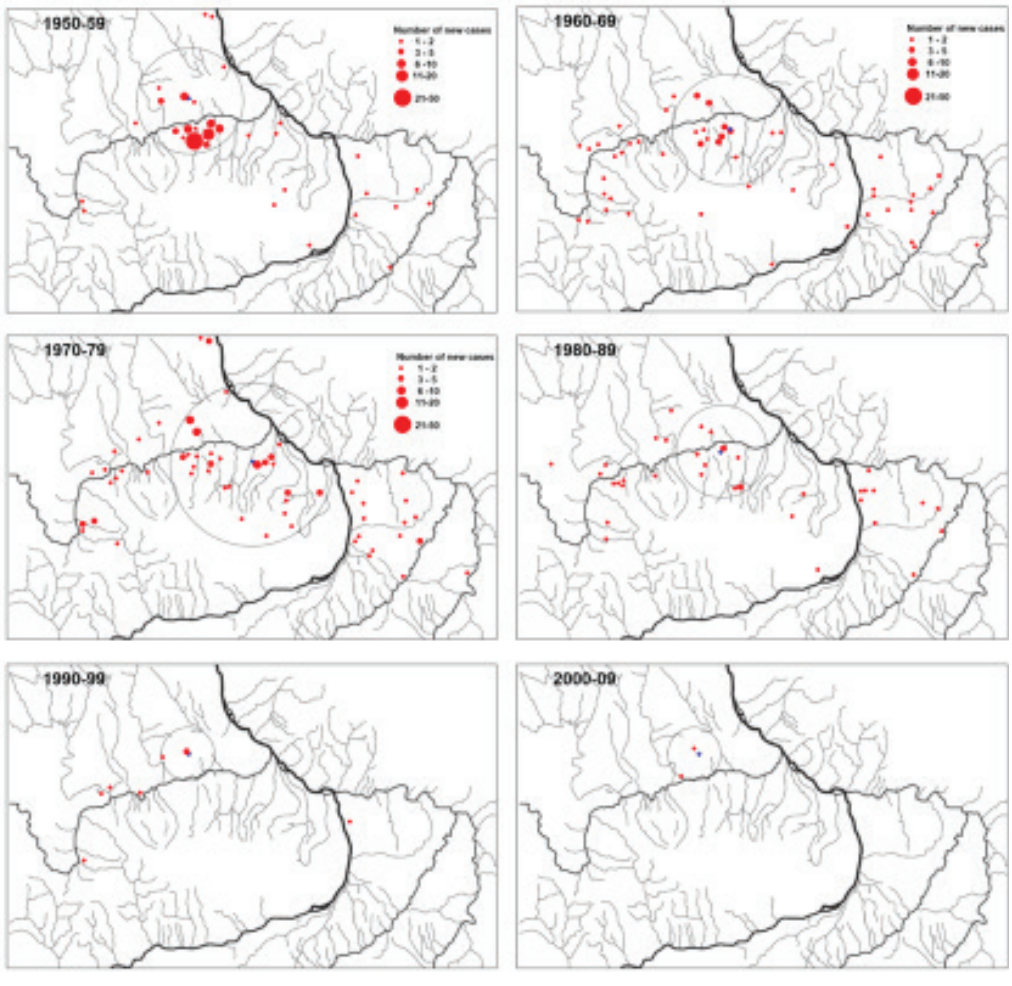

Fig. 2. Geographic location of settlements (red dots) in which new patients with Viliuisk encephalomyelitis were registered, by decades

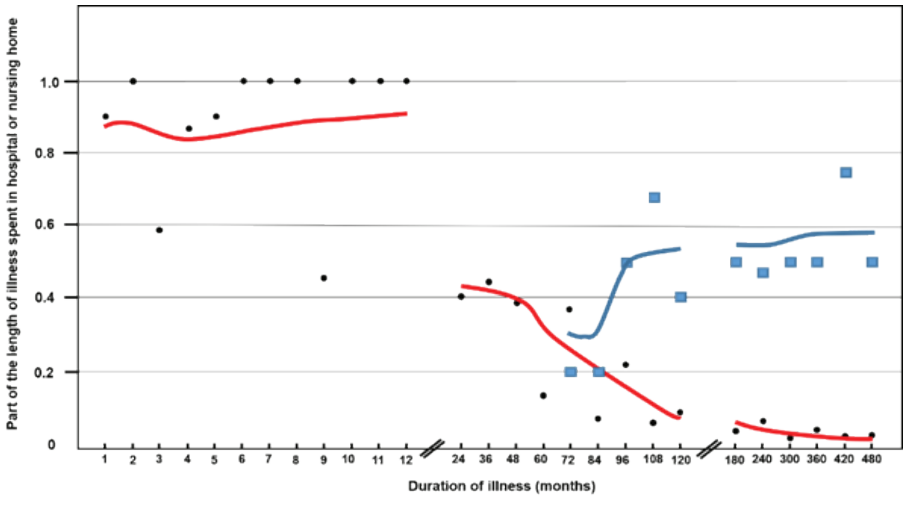

Fig. 3. Duration of hospitalization of patients with Viliuisk encephalomyelitis. Left panel: the curve represents the duration of hospitalization of VEM patients in the acute phase of illness in relation to the total length of the acute phase (n = 66). Middle panel: the red curve corresponds to the duration of hospitalization of patients with subacute VEM in specialized hospitals (including follow-up admissions); the blue curve reflects the length of stay in the Sosnovka Nursing Home in relation to the total length of their illness (n = 66). Right panel: the red curve shows the time patients with chronic VEM spent in specialized hospitals (including follow-up admissions); the blue curve represents the length of stay in the nursing home in relation to the total duration of illness (n = 111). Notes:1. Some patients who survived the acute phase of VEM who went on to develop subacute or chronic VEM status may have been counted more than once. 2. The dots mark the duration of hospitalization; the squares – the length of stay in the Sosnovka Nursing Home.

in the same household with the patient in 42% of cases but in only 29% of control families (p <0.05). Thirty-two percent of patients with VEM lived in a room of a house belonging to another family, in the same room with another family, or in a dormitory room, compared with only 13% of control families (p <0.01). In remote villages of the Viliuisk ulus, where the highest incidence of VEM was observed, people lived in houses that were much smaller than those in villages near the city of Viliuisk (p = 0.03). In the 1950s, there was only one public bath in the entire Viliuisk ulus; by the 1970s, 23 public baths were registered, all of them open only in the winter and then operating only two or three times a week. In the 1990s, the number of baths increased several times and 40% of them were private. By 2007, 42% of patients with VEM versus 92% of control families lived in dwellings with private baths (p <0.025).

Over the past eight decades, the Republic of Sakha (Yakutia) has made significant progress in its healthcare sector. Smallpox was eradicated in 1937, typhoid fever in 1938, malaria and trachoma by the late 1950s, poliomyelitis in the early 1960s, and leprosy in 1969. The incidence of diphtheria has become insignificant, and the incidence of measles has decreased by 7.5 times. The availability of health care in settlements of all sizes has grown.

Conclusion. Although the etiology of VEM, its origin and mechanisms of transmission remain poorly understood, available data characterize VEM as a transmissible disease that broke through the confines of a geographically isolated indigenous population living around *Lake Mastakh* to cause an epidemic of a severe neurological disease involving hundreds of victims. The aggregation of cases in households and small villages suggests that VEM was likely to have been transmitted through prolonged close intra-household contact, the same mechanism involved in transmission of other chronic infectious diseases such as tuberculosis and leprosy. There is a suspicion that the causative agent of VEM probably circulated in nature before it acquired the ability to infect people and pass from person to person [9]. Persistent efforts to reduce close contacts between patients with acute and subacute VEM and the surrounding population was followed by a marked decrease in incidence of VEM, which slowly declined in the 1980s and 1990s and finally reached zero in the 2010s. No new cases of VEM have been reported since 2012. Socio-demographic changes in the Republic of Sakha (Yakutia) increased the standard of living, modernized traditional lifestyle, and improved nutrition, probably also contributing to the elimination of VEM. Taken together, these efforts might well have prevented yet another emerging infectious disease from spreading globally. Since there is no certainty that the epidemic will not resume under some unknown conditions, it would be prudent to continue researching the collected materials and to maintain the qualifications of the doctors responsible for diagnosing VEM.

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