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PROBABLE CAUSES OF VILYUI ENCEPHALOMYELITIS. FACTS OF THE HISTORY OF STUDY AND REASONING

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ABSTRACT

Vilyui encephalomyelitis (VEM) is a degenerative disease of the central nervous system, in acute form, manifested by meningoencephalitis, which ultimately tends to develop in the form of long-term chronic progressive panencephalitis. Rapidly progressive cases of the type of fatal slow infection lead the patient to death ranging from 2 months to 6 years. We have developed a new hypothesis about the anthropozoonotic nature of the disease, based on an analysis of the sudden stop of the incidence of VEM.

The **purpose** of this article is to provide a scientific basis for this hypothesis. We analyzed extensive data from clinical observations of VEM patients, according to archive data stored at the former NEFU Health Research Institute, as well as a review of scientific publications on VEM over the past 30 years. A long-term study of VEM demonstrated the validity of the infectious hypothesis VEM. However, when considering possible causes, detailed studies were not conducted due to the detection of antibodies in several different candidate viruses in small, statistically unreliable groups of patients. The putative etiological agent was not reliably isolated. Attempts to infect various laboratory animals were not successful. Clinical and epidemiological data indicated the likelihood of horizontal transmission of the suspected pathogen from person to person. We compared the dynamics of the VEM epidemic process and found that the time of the disappearance of its epidemics coincides with the period of disappearance of some species of rodents and birds, potential carriers of the VEM virus in biocenosis. This allows us to return to the assumption of the primary anthropozoonotic nature of the disease. It is not excluded that the epidemiological chain, broken by the current epizootics, can be revived in the context of the active introduction of modern man into the environment.

Keywords and abbreviations: Vilyui encephalomyelitis (VEM); Infectious hypothesis; Anthropozoonoses; Epizootic; Epidemiological chain; Biocenosis; Vilyuisk Human Encephalomyelitis virus (VHEV); Theiler-like virus; Theiler murine encephalomyelitis virus (TMEV); Bornavirus; California Virus encephalitis (Bunyaviridae); Viruses of Eastern and Western equine encephalitis (Alphavirus); the Virus encephalitis San Louis (Flavivirus); Immunoglobulinum G (IgG); Cerebrospinal fluid (CSF).

Introduction. For more than 60 years of study of Vilyui encephalomyelitis (VEM), the disease was reliably registered only in the indigenous population of Yakutia (Sakha, Evens, Evenks), mainly living in remote and sparsely populated rural areas. In archival sources, materials of isolated cases of probable VEM of people of another ethnic group (mostly Russian or mestizo) are available for discussion. Often Vilyui encephalomyelitis starts with high temperature (39-40°), chills, painful headache, muscle aches and extreme fatigue. In chronic form, progressive dementia, speech disorder, lack of facial expressions, violation of motor function prevail. In severe progressive cases, the disease leads to death within 3-5 years [7].

In the monograph "Vilyui encephalomyelitis" [2] summarizes the main achievements in the study of VEM. It is indicated that the main reason for the nomination of several mutually exclusive or partially interfering hypotheses about the origin and pathogenesis of VEM is the uncertainty and often incomplete results of studies that could potentially fully confirm or refute the assumptions. "Each hypothesis was proposed by bright authoritative scientists who did not have a great desire to listen to opposing opinions or work in a direction that would allow to refute their own hypothesis. Therefore, the discussion of the 1970-ies, whatever they may be interesting, has not led to the solution of the problem." But most importantly, the causative agent of VEM is not isolated. In accordance with the latest research in the field of pathogenesis of VEM and other chronic inflammatory diseases of the Central nervous system, immunopathological mechanisms were identified, which apparently play a crucial role in the development and maintenance of a long inflammatory process. "Detection of intrathecal production of oligoclonal IgG, which is consistently present for 3 decades after the onset of the disease in the subacute and early stages of the chronic phase, i.e. at a time when the inflammatory process is still active [5,20], as well as the Association between VEM and rare variants in the IFN-G gene [14] and the probable role of *IFN-G* in the pathogenesis [2, 14] characterize VEM as a disease with a pronounced immunopathological component. This leaves the assumption that an infectious agent causes destruction of neurons on the background of insufficiency of the immune system, most likely. Research in this direction should be continued" [2]. Over the year, 26352 patients are hospitalized with encephalitis in the USA, of which 49.7% of the etiology of the disease remains unspecified [15]. In the Russian Federation, from 15,000 to 32,000 patients with inflammatory diseases of the central nervous system, including in Yakutia, from 50 to 80 cases, almost all of them can be considered cases with unexplained etiology. Searches of candidate viruses among patients with encephalitis with an unclear etiology, while also being an unexplored problem, by no means eliminate the problem of Viluy encephalomyelitis from this list.

Materials and methods of the research. We analyzed the current state of the VEM problem in the available literature and materials of the archival database of the former Scientific-Research Health Institute of NEFU, including patient histories, reports of clinical and epidemiological observations since the 1960s, focusing on the following main areas of research: epidemiology, etiology, pathogenesis and features clinical manifestations.

Discussion. Based on the results of epidemiological studies conducted under the direction of L. G. Goldfarb, chief international coordinator of long-term VEM studies, it was shown with sufficient conviction that VEM is an infectious disease resembling slow infections.

This is indicated by the following scientific facts:

1. The nature of the spread and extinction of the disease [13], characterized by a marked evolution in the clinical picture of the disease from predominantly acute and subacute forms to predominantly long-current chronic forms, the spread of the disease first from the left Bank to the right Bank settlements of the Vilyui district and then to Central Yakutia, the disappearance of VEM from the Central.
2. Predominantly young age of patients - 30-34 years.
3. The spread of the disease

through migrants during the period of increasing morbidity in the 1960s - 1970s. According to N.I. Fedorova et al. [2] foci of VEM in some villages of Central Yakutia are formed around immigrants coming from high-risk areas, mainly Vilyui and Kobyai.

4. Aggregation of patients in families is equally common for families with sick blood relatives, and for families with sick adoptive relatives [2].

5. The case of the fatal disease of a laboratory assistant of European ethnicity after making herself a subcutaneous injection of the VEM patient's serum for suicidal purposes. The case of VEM was clinically confirmed by D.K. Gaidusek [17], the autopsy revealed morphological pattern between multiple sclerosis (MS) and VEM.

6. Aggravation of clinical manifestations of the disease in the case of secondary morbidity (for example, in families), reminiscent of the phenomenon of increased virulence in subsequent passages in the experiment [2].

7. Not a blood relatives and non-relatives cases of VEM in some families with prolonged household contact (a vivid example – a family of the VEM patient S.: his first wife became ill and died from VEM at the age of 37 years, and his second wife after his death 5 years later, also became ill and died from VEM 2 more women who had an extramarital affair with this man and 2 men colleagues (archives of the SR Institute of Health, NEFU, Yakutsk).

8. L. G. Goldfarb et.al, explained the seasonal distribution of the disease manifestation in the spring and autumn by the seasonal increase in agricultural work (plowing, hay harvesting, etc.) [2]. However, we would like to note that the highest incidence is observed in May. At this time, the village is not carried out massive agricultural work, but begins the spring hunting for waterfowl (May – for migratory ducks, June –for Turpan). The autumn peak of the disease August-September also coincides with the period of reduction of agricultural work and autumn duck hunting (August) and hares (September). According to the Yakut tradition, men hunt and women cut the prey, this fact is probably one of the main reasons for the high incidence of women in the initial stage of the VEM epidemic.

9. The difference in the number of sick men and women during the period of increase and decline in the incidence of VEM: the predominance of women in the first period and the equalization of the gender difference in the second period of morbidity [2], also, in our opinion, it is most likely due to a change in the predominant ways of transmission. In the first period, the transmission of infection probably occurred when cutting the carcasses of infected animals, and in the second - household way from a sick person to a healthy one.

The search for the causes of the disease revealed in the serum of patients with VEM antibodies against a variety of infectious agents. In discussing these issues, we came to the conclusion about the selection of candidates for an infectious agent of VEM and decided to include in this list the following viruses: Vilyuisk Human Encephalomyelitis virus (VHEV); Theiler-like virus (TMEV); Bornavirus; California Virus encephalitis (Bunyaviridae); Viruses of Eastern and Western equine encephalitis (Alphavirus); the Virus encephalitis San Louis (Flavivirus) [2]. Our experience in studying the causes of VEM and literature analysis suggests the following ways of transmission:

- Vector-borne: arthropod Diptera (mosquitoes), ticks, fleas, lice, bugs. The existence of a vector-borne route of transmission allow you to suspect the findings of antibodies to the causative agents of encephalitis, is transmitted by these viruses: California encephalitis (Bunyaviridae), Eastern and Western equine encephalitis (Alphavirus), encephalitis San Louis (Flavivirus);
- Contact: long household contact (blood, saliva?), sexual ("some village epidemics" according to clinical and epidemiological observations).
- Parenteral: blood transfusion. For example, patient P., from village Dalyr, Ust-Aldan, dates of birth and death 1955 -1993, the onset of the acute VEM in November 1984, but 6 months before the disease he had got a blood transfusion because of a serious knife wound. Manifestation of VEM with fever, meningeal symptoms, psychotic disorders, coma, (in liquor protein 330 mg/l, lymphocytic cytosis 27 cells) stage of intermission after acute VEM lasted 5 months. After that, the exacerbation of the disease manifested in the form of subacute VEM with the rapid development of a typical clinical syndrome with dementia, spastic tetraparesis, dysarthria. The duration of the disease was 9 years (Archive of SR Health Institute, NEFU, Yakutsk).

The spectrum of antiviral antibodies in the serum of patients with VEM allows one to suspect involvement in the development of the disease by a zooanthropic infection transmitted through the blood, probably by contact or transmission. We found a coincidence of the peak incidence and disappearance of the epidemic outbreak of VEM in Yakutia with the disappearance of the common rodent form of *Arvicola terrestris* and the local population of migratory ducks, *Anas formosa*, the main prey of spring hunting of the local population, and the elimination of malaria in Yakutia.

Arvicola terrestris

This animal disappeared on the territory of Yakutia in the early 1990s for an unknown reason. Epizootics is not excluded. *Water (Field) vole* was widespread and was numerous throughout Russia. In Soviet times, people hunted up to 5 million skins of *Field voles* per year [5]. Until the middle of the XVIII century *Arvicola terrestris* served as a delicacy of the indigenous population [1] and this custom was eradicated in connection with the adoption of Christianity. The students were engaged in hunting on these animals, some champions for the season were mined up to 1000 skins. Rodents have had daring temper and often bite the young hunters. Of course, most of the mothers and sisters helped to remove the skin of the rodent. The prevalence of the species in Yakutia has been declining since the 1980's. "The number of *Water voles* in the last 20 years are very low, the last time we caught them in the Lena district in 2002, also they appeared in the vicinity of Yakutsk . Residential burrows were found in the autumn of 2017, but no animal could be caught. Also there were noted traces of stay in the Amginsky district in July 2018" as it known from personal message of Candidate of Biology O.I. Nikiforov. "In the vicinity of Yakutsk for 20 years did not come across a *Water vole*. I with students in recent times caught them in about 1995. The decrease in its population, with occasional appearance in some regions observed throughout Russia. For *Water voles* have established a clear link with tularemia" – private message from Doctor of Biology E.G. Shadrina. *Arvicola terrestris* is a reservoir of the following infections: tularemia, Omsk hemorrhagic fever, leptospirosis, some vector-borne infections, etc. In addition, in the 1980s., *Field mice* in the homes of villagers began to be replaced by *House mice* due to the mass importation of animal feed.

Elimination of malaria. The fight against malarial mosquitoes in Yakutia was launched malarial stations, organized for the first time in 1936. The 1964th is the year of eradication of malaria in Yakutia [9]. Antibodies against malarial Plasmodium (weakly positive) were found in 100% of the examined patients with VEM. On the other hand, according to clinical and epidemiological studies,

only three patients with VEM suffered from malaria [2]. *Isn't the resistance to malaria a predisposing factor of VEM? This hypothesis should also be tested.*

The etiology of VEM

Attempts to isolate the infectious agent by inoculation of biological material of patients with VEM were not successful. Two successful attempts to isolate infectious agents E.S. Sarmanova et al. [8] and A.S. Karavanov et al. [3] up to the present time have not been recognized as the cause of VEM.

What is the cause of failure? We see three reasons for this (from the standpoint of the infectious nature of the disease):

1. Perhaps, materials from the patients inoculated experimental animals did not contain the virus, due to the fact that the replication of the virus occurs only in the acute period of the disease, when fever. The Human organism is likely to rapidly eliminate the virus, but the further development of the disease is supported by unknown infectious virus molecules, probably incorporated into the genome of infected cells of the patient, or as in the case of the experimental model of TMEV infection, the virus persistence persists in very low titers [18];
2. There is a possibility of having another mechanism of the infection. In the case of VEM, we are dealing with a completely new, previously unknown mechanism of transmission of an infectious agent, and the infectious agent is a previously unknown molecule or agent of protein nature;
3. Only Homo sapiens can be susceptible to the virus.

Over 60 years of study history of VEM, the efforts of an international group of researchers have been directed to the search for an infectious agent in accordance with Koch's postulates. It should be noted that D.K. Gaidushek and B. Marshall with R. Warren received the Nobel Prizes, proving the infectious nature of the Kuru and gastritis in accordance with Koch's postulates. But in the case of VEM, these postulates do not work. In our opinion, the fact that the main contender for the cause of VEM HMEV has a special weapon in the form of unstructured protein L * draws attention to itself. But articles appeared in a number of reputable international publications confirming the contaminant nature of the HMEV virus [12]. After these reports, all studies in the world on this virus were probably discontinued, but the Russian virologist, prof. G.G. Karganova isolated a new virus from the canned same material E.S. Sarmanova [6]. According to the RNA sequences, this virus differs from HMEV (G.G. Karganova's personal communication). We had very good reasons to check the Taylor-like viruses for the etiology of VEM. It should be noted that, until now, metagenomic studies, analysis of the degree of DNA methylation, sequencing of RNA, full-genome sequencing of DNA, mtDNA and identification of proteins in the brain tissue of a patient with VEM have not been studied. The exomic sequencing of the genome of VEM patients in the USA and in Russia did not yield breakthrough results [2]. In addition, studies to determine the antigenic specificity of oligoclonal IgG CSF in patients with VEM with antigens of candidate viruses have also not been conducted.

Conclusion. There is compelling clinical, pathological, and epidemiological evidence that VEM is a contagious infectious disease with a prevalent pattern of latent and chronic infections. The intensive search for the infectious agent VEM has not been crowned with success, but the possibilities of finding the causes of VEM using modern research methods have not been exhausted.

In this paper, we put forward an assumption about the anthropozoonous nature of the disease, it is assumed that under the guise of VEM can manifest clinically similar neuroinfections caused by a number of previously undetected viruses in the region, carriers of which can be some animals and birds of biocenosis.

The following rodents and mammals may be likely intermediate hosts of VEM candidate viruses: medium shrew *(Sorex caecutiens)*, water vole *(Arvicola terrestris)*, house mouse *(Mus musculus)*, field mouse *(Apodemus agrarius)*, Siberian chipmunk *(Tamilas sibricus)*, ermine *(Mustela erminea)*, weasel *(Mustela nivalis)*, squirrel *(Sciurus)*, hare white *(Lepus timidus)*. From migratory ducks: pintail *(Anas acuta)*, Siberian turpan *(Melanitta fusca stejnegeri)*, teal cloctoon *(Anas formosa)*. The choice of species for the study was made on the basis of the following criteria: they are reliably established reservoirs of candidate viruses, are related to the economic activities of the population of endemic VEM areas, or migratory birds from regions where VEM candidates are registered. Mice and water voles are TMEV reservoirs, but on the territory of Yakutia which Taylor strains of such viruses circulate is not known. Water vole and chipmunk were the subject of hunting until the 60s. and animal skins were harvested by Rural Consumer Society units. Ermine and squirrel up to the present are hunting animals. Weasel and ermine feed on voles, so their probability to be a TMEV reservoir is high. The literature describes three deaths of people infected with Born virus from a variegated squirrel in Germany [19]. In Alaska, strains of California encephalitis have been isolated from hares, and antibodies to the virus have been isolated from Indians [11, 16]. From the rodent the medium shrew has been isolated of a Hunt virus called the Lena river virus (LNAV), but its role in human disease has not been elucidated [21]. Of migratory ducks, the *Anas Formosa* wintering grounds are China, Japan, and Korea, where cases of human occurrence of California and Japanese encephalitis are recorded, the Siberian turpan also overwinter in these places. The most common and highly migratory duck is the pintail. She is found everywhere. It is known that it flies to India and other countries of Southeast Asia for wintering, including Sri Lanka and Borneo, which is probably why this duck can bring the viruses Eastern and Western equine encephalitis, and St. Louis encephalitis to East Yakutia. In addition to the California encephalitis virus, the Syr-Daryinsky virus and other Taylor-like viruses in the territory of Northern Eurasia, the VEM candidate viruses were not registered [21]. In connection with the above, the search for these viruses for the first time can ascertain the natural foci of their circulation, which is of not only theoretical but also practical importance for the prevention of diseases caused by these viruses.

Thus, funding research on clarifying the circulation of VEM candidate viruses and similar neuroinfections in zoonotic foci of a region that is endemic in VEM is an urgent problem for Yakutia. Such work will undoubtedly play a significant role in ensuring the biological safety of the Russian Federation.

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The authors deny the emergence of conflict in the course of the study.

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