

Viliuisk Encephalomyelitis

Neil M Renwick¹, Lev G Goldfarb^{2*}, Vsevolod A Vladimirtsev³, Fedor A Platonov³ and David M Asher⁴

¹Department of Pathology and Molecular Medicine, Queen's University, Kingston General Hospital, Canada

²National Institute of Neurological Disorder and Stoke, National Institute of Health, USA

³Institute of Health, M.K. Ammosov North-Eastern Federal University, The Russian Federation

⁴US Food and Drug Administration, Silver Spring, Maryland

***Corresponding author:** Lev G Goldfarb, National Institutes of Health, Maryland, USA, Tel: 301-219-2920; Email: GoldfarbL@ninds.nih.gov

Published Date: June 02, 2016

SUMMARY

Viliuisk encephalomyelitis is a unique disease occurring in the Sakha population of Northeastern Siberia. Viliuisk encephalomyelitis is always fatal, with some patients dying during the acute encephalitic phase of illness; those surviving the acute phase develop progressive dementia, rigidity and spastic quadriplegia as part of a more prolonged pan-encephalitic syndrome. The disease is characterized histologically by multiple widespread micronecrotic foci with marked inflammatory reaction and subsequent gliosis throughout the cerebral cortex, basal ganglia, cerebellum, and brain stem. The acute febrile onset with cerebrospinal fluid pleocytosis, increased total protein, and inflammatory neuropathology indicate that Viliuisk encephalomyelitis is probably an infectious disease, but the causative agent has not been identified. Initially detected

90 years ago in a small mixed Sakha-Evenk population of the mid-Viliui region, the disease subsequently spread southeast to densely populated areas around the capital city of Yakutsk. The occurrence of secondary Viliuisk encephalomyelitis cases in households and the introduction of the disease by migrants into previously unaffected populations indicate that the disease is horizontally transmitted in a setting of a long intra-household contact. Although there has been a recent decline in the number of cases, increasing travel may result in further spread of this fatal disease to susceptible individuals in other regions of the world.

Keywords: Viliuisk encephalomyelitis; Sakha (Yakut) Republic; Eastern Siberia; Viliui river; Inflammatory brain syndrome

INTRODUCTION

Viliuisk Encephalomyelitis (**VEM**) is an enigmatic neurological syndrome that mostly affects the indigenous Sakha people of the Sakha (Yakut) Republic, The Russian Federation. This complex fatal disease was initially confined to a rural population living near the remote Viliui District in Northeastern Siberia [1,2]. However, by the 1970s, the disease had spread to a larger geographic area, including more densely populated areas of the central Sakha Republic [3]. The epidemic nature of VEM caused considerable medical concern and administrative alarm.

To understand and prevent VEM, systematic studies of affected individuals were initiated through Dr. Prokopiyy A. Petrov, then a neurologist in the Viliuisk District Hospital, in 1951; Dr. Petrov is credited with the discovery and first detailed clinical description of VEM. Later, as Minister of Public Health and Professor of Neurology at Yakutsk University, Dr. Petrov led a series of research expeditions to the Viliuisk region. During 1954-1957, a vast amount of data was accumulated on clinical manifestations, neuropathology, epidemiology of VEM and a putative etiological agent ("Viliuisk virus") was isolated [4].

With the VEM epidemic showing no signs of abating, surveillance was expanded to cover the entire Sakha (Yakut) Republic. In 1967, a specialized VEM clinic was opened in the capital city of Yakutsk; patients were thoroughly assessed and experimental treatments were tested under the expert guidance of Dr. Afanasiy I. Vladimirtsev [5]. During 1969-1982, a comprehensive study of VEM etiology and epidemiology was conducted by Dr. Mikhail P. Chumakov from the Institute of Poliomyelitis and Viral Encephalitides in Moscow; VEM diagnostic criteria were revised substantially because several other diseases, notably Hereditary spinocerebellar ataxia, were inadvertently classified as VEM [6].

Since the 1990s, the incidence rate of VEM has gradually declined. Several hypotheses have been proposed about the cause and nature of the VEM epidemic in the Sakha (Yakut) people; however, these remain speculative due to elusive etiology. Here, we summarize multi-decade clinical and research findings on VEM to draw attention to this enigmatic disease in case of re-emergence.

PATIENTS AND THE AFFECTED POPULATION

The vast sparsely populated territory of the Sakha (Yakut) Republic is located in Northeastern Siberia, the coldest area in the Northern hemisphere (Figure 1). The Sakha people originated from a nomadic Central Asian tribe that migrated, under pressure of Mongol expansion, to the North-Siberian plains 600 to 900 years ago [7]. The newcomers brought to Siberia a dialect of Turkic language and cattle/horse breeding culture. By the time of Russian colonization at the beginning of the 17th century, the Sakha still lived in a small area in the Lena-Aldan valley (currently central Yakutia) with Tungus (Evenks) and Evens, reindeer herders and hunters, occupying the lands around Sakha settlements. The Sakha assimilated the neighboring indigenous populations; remnants of Evenk tribes can still be found in the northern parts of the Viliui valley. Following centuries of Tsarist and Soviet government restrictions on the movements of people, the local population was only allowed to migrate to centrally located industrial centers after World War II when the development of Siberian resources significantly intensified. The Sakha-speaking population has now reached 500,000 people.



Figure 1: Northeastern Asia. Highlighted - Sakha (Yakut) Republic, Russian Federation.

The VEM cohort consists of 337 patients with definite VEM classified using clinical criteria approved by the VEM Diagnostic Committee at the Institute of Health, Yakutsk [8]. In 1999, an electronic database, containing extensive demographic and clinical information on VEM patients,

was established and maintained by the Clinical Neurology Department at the Institute of Health. VEM studies were performed in accordance with human subjects research protocols approved through the Institute of Health of the Republic of Sakha and the U.S. National Institutes of Health.

CLINICAL MANIFESTATIONS

Analyses of clinical manifestations in our cohort indicate that VEM is a complex disease. In 210 (62%) of 337 VEM patients, disease onset was sudden and rapidly progressive over several days or weeks. In 127 (38%) patients no acute phase of illness was identified; presenting symptoms included progressive limb weakness, malaise, unstable movements and gait abnormalities, and speech disturbance, often noticed by family members and fellow villagers rather than by the patient. Subsequent long-term monitoring showed that three clinical variants of VEM can be recognized:

1) Rapidly progressive (acute) VEM characterized by: i) prolonged fever (ten or more days), ii) headache of increasing intensity, iii) altered consciousness (coma, delirium), iv) clinical features of meningoencephalitis and/or cerebrospinal fluid (CSF) lymphocytic pleocytosis with increased total protein concentration, and v) spastic paresis. Of 21 patients with acute VEM, 18 (86%) were comatose at presentation and remained in a state of reduced awareness for days to months. All had persistently high (40-41°C) fevers lasting 2-6 weeks, neck stiffness, and a positive Kernig's sign; cranial nerve dysfunction, including ptosis, diplopia, and strabismus, were also frequent findings. Despite recovering consciousness, sustained neurological impairment, including cognitive decline, bradykinesia, muscle rigidity, dysarthria, hyperactive deep tendon reflexes, spastic quadriparesis, and generalized seizures, was evident. This clinical variant was relentlessly progressive and all 21 patients died within a year of disease onset.

2) Slowly progressive (subacute) VEM characterized by: i) a documented history of meningoencephalitis, ii) progressive dementia, iii) dysarthria, iv) pyramidal and extrapyramidal signs, v) CSF lymphocytic pleocytosis with elevated total protein concentration, vi) CSF oligoclonal IgG bands, vii) diffuse brain atrophy on neuroimaging, and viii) a slowly progressive illness (typically, 1-6 years duration). Of 76 patients with subacute VEM, 57 (75%) had a characteristic clinical course (Figure 2).

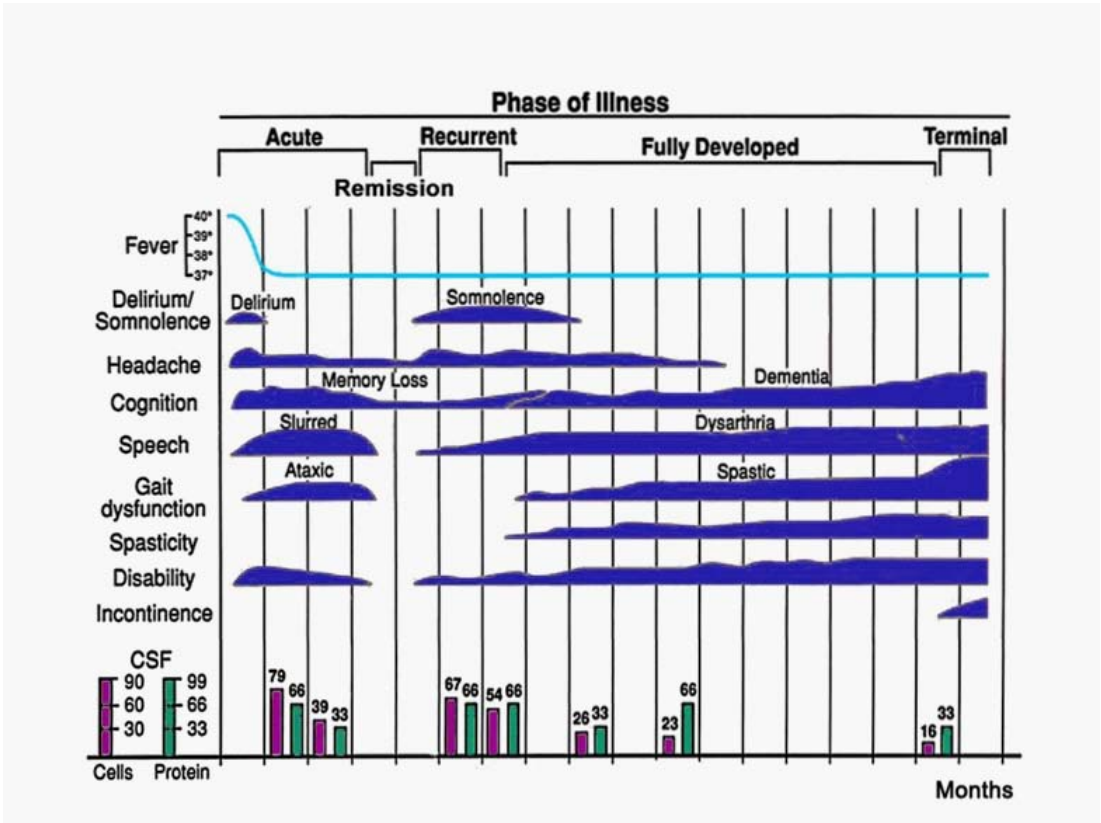


Figure 2: Clinical chart of a representative patient with slowly progressive (subacute) Viliuisk encephalomyelitis. The 38-year old patient was admitted with delirium, fever, chills, headache, myalgia, nausea and frequent vomiting. He remained mentally and physically slow, shaky and had neck muscle stiffness and a positive Kernig’s sign. After ten weeks, he recovered adequately to return to work. However, after several weeks of relative stability, his speech became slurred and he experienced memory lapses; on examination, he had hyperactive deep tendon reflexes, bilateral Babinski sign, decreased muscle strength predominantly in distal lower limb muscles, and a markedly spastic gait. Within several months, his cognitive abilities further declined, his speech became severely dysarthric, and he walked with great difficulty due to spastic quadriparesis. Sphincter dysfunction was another feature. The disease progressed relentlessly thereafter and he died 17 months after the onset of illness. CSF cell counts and total protein concentrations were elevated throughout the entire illness.

Disease onset was similar to that of acute VEM with gradual subsidence of fever, headache, and somnolence and a period of clinical remission lasting 2-12 (mean 6.1) months. However, recovery was incomplete; behavioral changes, pain in the extremities, muscle rigidity, and clumsiness when performing complex motor acts persisted. A progressive syndrome consisting of dementia, characteristic dysarthric speech, pyramidal quadri- paresis or lower para-paresis, and associated

bradykinesia, postural instability and cogwheel rigidity slowly developed. Ophthalmoplegia, dysphagia, choreiform movements, and hypothalamic dysfunction were present in some patients; cerebellar symptoms were rare and sensory deficits were absent. Of particular note, muscle stiffness and spasticity steadily progressed with patients developing a characteristic stout frame, expressionless face, and complacent behavior termed “bokhoror” by other villagers. Despite pronounced spasticity and stiffness, patients remained strong and able to walk considerable distances. In the terminal stages of disease, patients were globally impaired, appearing mute, unable to communicate, and incontinent. Death typically resulted from respiratory or circulatory failure 13-72 months after disease onset at an average age of 40 years.

3) Chronic VEM characterized by: i) a documented history of meningoencephalitis or gradual onset of symptoms, ii) dementia (or memory impairment), iii) dysarthria, iv) pyramidal and extrapyramidal signs, v) CSF oligoclonal IgG bands (typically present up to 20-30 years after onset), vi) diffuse brain atrophy on neuroimaging, and vii) prolonged duration (> 6 years) with minimal progression over the preceding three years. Of 240 persons with chronic VEM, 132 (55%) patients first experienced acute or subacute VEM whereas the remaining 108 (45%) patients presented with gradually increasing difficulty in pronouncing words and walking. In either situation, chronic VEM, with characteristic intellectual decline, bradykinesia, and muscle rigidity, ensued. Death typically resulted from trauma, pneumonia, renal failure, or infection at an average age of 55 years.

Frequency of Clinical Variants

The proportions of acute, subacute, and chronic VEM changed over the course of the epidemic. Acute and subacute VEM cases dominated early in the epidemic [2], while equal numbers of acute/subacute and chronic VEM cases were present in the 1970s, and most (93%) VEM cases were chronic in the 1980s (Table 1). The increase in disease duration was partly due to improved patient care and extensive therapeutic interventions in acute and subacute periods, thereby reducing mortality from complications.

Table 1: Proportion of clinical variants at different stages of the Viliuisk encephalomyelitis epidemic.

Decades	Acute and Subacute VEM	Chronic VEM	P-value
1970-1979	58 (49%)	61 (51%)	
1980-1989	3 (7%)	39 (93%)	< 0.05

Cerebrospinal Fluid Analyses

CSF laboratory values were available for 188 (56%) of 337 patients with definite VEM. In 21 acute VEM cases, cell counts averaged 25 per mm³ throughout the illness, and all except two patients had elevated total protein concentrations. In 42 (81%) of 52 subacute VEM cases, cell counts averaged 30 per mm³ during the first year of illness and failed to normalize by the 72nd

month after disease onset; the total protein concentration was increased in 34 (65%) of these patients. In chronic VEM, cell counts were moderately increased to 11-15 per mm³ in 31 (69%) of 45 tested patients within a 72-month time period after disease onset, but in 15 (33%) of 45 patients cell counts increased significantly at least once between the 72nd and 120th months, reaching an average of 41.5 cells per mm³, then returning to normal levels after the 120th month of illness. Periodic exacerbations of neurological symptoms were observed in some patients with chronic VEM. Moderate increases in cell count and elevation in total protein concentration indicate an inflammatory pathomechanism.

Neuroimaging performed in later stages of VEM revealed communicating hydrocephalus, lateral extension of the third ventricle, and diffuse cortical atrophy, mainly in the fronto-parietal-temporal areas (Figure 3).

Fig. 3

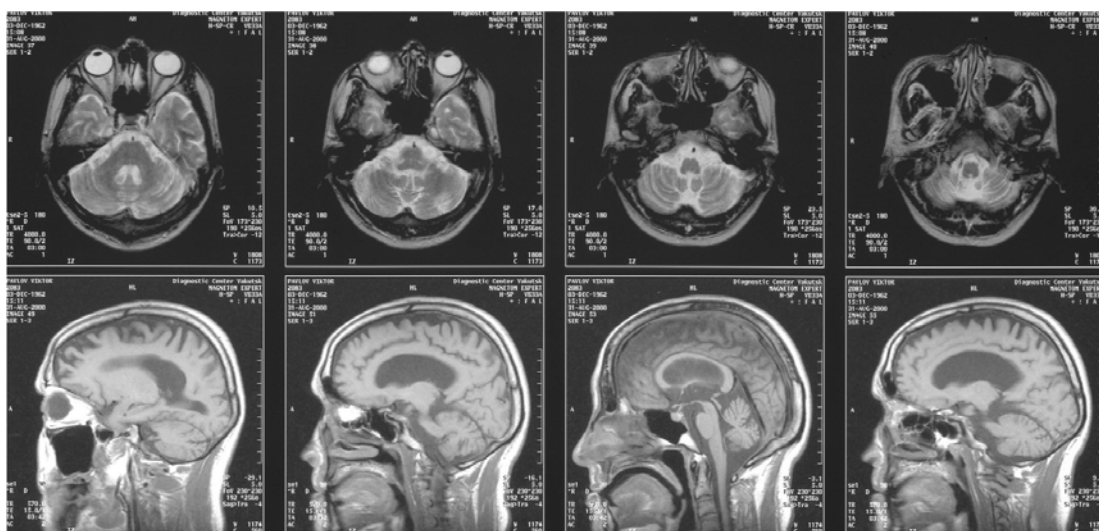


Figure 3: Brain Magnetic Resonance Imaging of a 38-year-old patient with subacute Viliuisk encephalomyelitis 12 months after disease onset. Prominent diffuse cerebral atrophy.

Electroencephalographic recordings show ongoing epileptic activity in some acute and subacute VEM cases. In chronic VEM, there was diffuse lowering of electric potentials, mainly in the frontal and parietal regions with minimal hemispheric asymmetry; alpha rhythm was replaced by a low-amplitude, irregular beta rhythm with superimposed polymorphic slow waves.

Isoelectric focusing with immunoblotting detected oligoclonal IgG bands in the CSF but not serum (Figure 4) in 17 (94%) of 18 patients with clinically/histopathologically confirmed subacute/chronic VEM [9]. Presence of IgG bands in the CSF but not serum had a diagnostic sensitivity of 93% and specificity of 80% for VEM [10].



Figure 4: Isoelectric focusing with immunoblotting for the detection of oligoclonal IgG in the cerebrospinal fluid (CSF) of a patient with subacute Viliuisk encephalomyelitis. Left lane – serum, right lane – CSF.

NEUROPATHOLOGY

Neuropathological examination of fatal acute VEM cases showed cloudy and diffusely edematous meninges consisting of a mixed inflammatory infiltrate of mononuclear, plasma, and polymorphonuclear cells, particularly in areas overlying affected cortical regions. In the brain parenchyma, widespread micro-necrotic foci up to 0.4 mm in diameter (Figure 5A), consisting of condensed eosinophilic granular material surrounded by inflammatory infiltrates, were observed throughout the cerebral cortex, basal ganglia, cerebellum and brain stem, with less frequent involvement of the subcortical white matter [11].

Neuronal destruction (Figure 5B) in affected areas, as well as diffuse neuronal loss outside these areas (Figure 5C), was seen. Perivascular inflammatory cuffs (Figure 5D) were widespread in affected areas and contained predominantly activated T-lymphocytes, Natural Killer (NK) cells, and NK-like cytotoxic T lymphocytes, with few macrophages [12]. Acute necrotic and partly

organized lesions were seen in the ventral and dorsal gray and white matter of the spinal cord, with a predilection for anterior horn motor neurons. Special stains for organisms were negative. No viral particles were identified through electron microscopy [11].

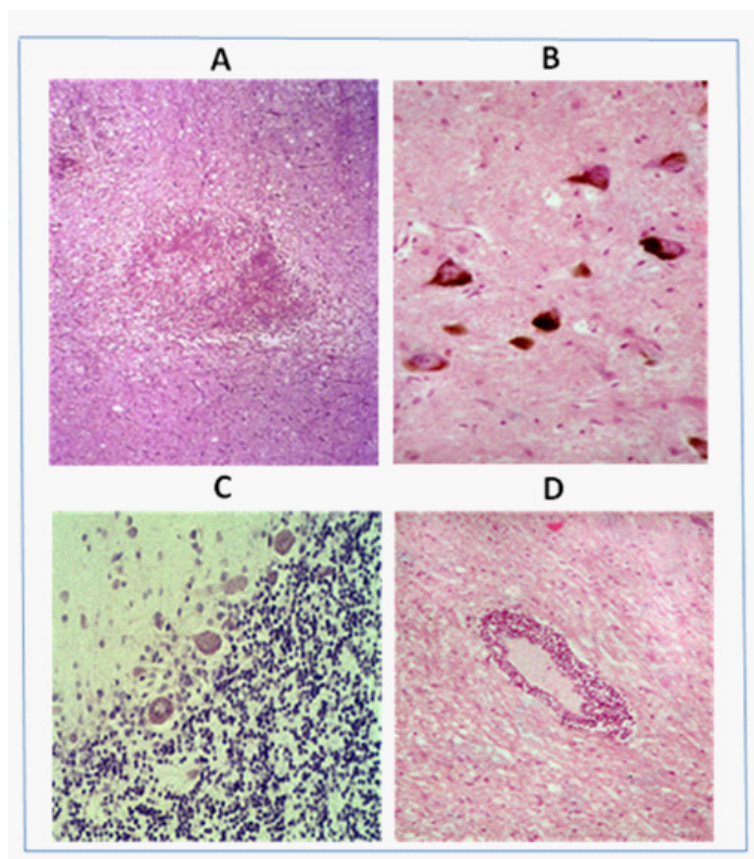


Figure 5: Histopathological studies of acute Viliuisk encephalomyelitis. A. Typical encephaloclastic focus showing central necrotic debris, palisaded by microglial cells, macrophages and lymphocytes. Cerebral cortex. Hematoxylin and eosin, x160. B. Dystrophic changes in neurons. Subcortical nucleus. Hematoxylin and eosin, x200. C. Lysis of Purkinje cells. Cerebellum. Hematoxylin and eosin, x200. D. Massive perivascular infiltration with lymphocytes. Cerebral white matter. Hematoxylin and eosin, x200.

In subacute VEM cases, necrotic foci within the brain parenchyma were less frequent. The ratio of active, organizing, and lytic foci varied from case to case with some lesional confluence leading to extensive destruction (Figure 6A) in all cortical laminae, reactive gliosis and secondary demyelination in the underlying white matter; this active inflammatory process lasted no less than six years [13].

In chronic VEM cases, the meninges were fibrotic and adherent with minimal residual inflammation. The cerebral cortex was atrophic (Figure 6B) and there was severe neuronal loss.

Micronecrotic foci were replaced by solitary or confluent microcysts rimmed by gliosis. Scattered gliosed and lytic foci were also seen in the basis pontis, pontine tegmentum, medulla and gray matter of the spinal cord [11,14,15]. In some cases, the coexistence of fresh necrotic lesions and healing scars appeared to be a histological basis for exacerbations in patients with chronic VEM.

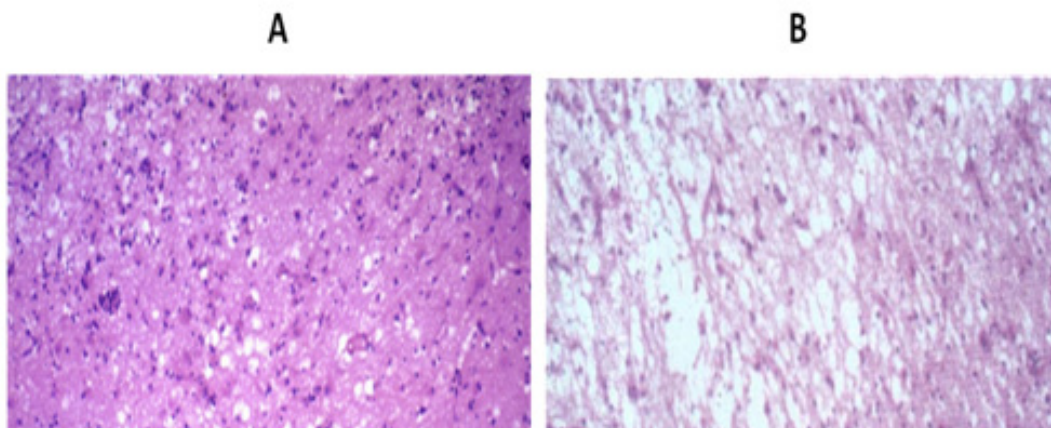


Figure 6: Histopathological studies of subacute and chronic Viliuisk encephalomyelitis. A. Parenchymal and perivascular collections of lymphocytes, neuropil lysis, and neuronal loss. Cerebral cortex. Hematoxylin and eosin, x160. B. Lysis, spongiosis, and minimal residual inflammation. Cerebellar cortex. Hematoxylin and eosin, x160.

The results of multi-year postmortem studies on 66 patients indicate that VEM is a distinct neuroinflammatory process with the degree of inflammation corresponding to the acute, subacute, and chronic variants of VEM [11, 13,15]. The neuroinflammatory reaction consisted of necrotic foci surrounded by a mixed acute and chronic inflammatory infiltrate and the presence of perivascular lymphocytic cuffs in affected areas in acute/subacute VEM; this process “burns out” in chronic VEM although active necrotic foci in prolonged disease suggests that reactivation may underlie symptom exacerbations [11].

EPIDEMIOLOGY

Patient Demographics

Most VEM patients in our cohort were ethnic Sakha with the exception of six Evenks (Tungus) and eleven individuals born in mixed Sakha (Yakut)-Evenk (Tungus) marriages. All patients were born in small villages. A substantial number, 127 (59%) of 215 with a known day or week of disease onset, fell ill in May-August.

Trends in Incidence Rates

The average annual incidence rate of VEM was 3.5 (95% confidence interval [CI] = 2.5-4.7) cases per 100,000 population in 1940-1949. This rate increased to 8.8 (CI = 8.0-9.6) in 1950-1959 and remained elevated at 6.4 (CI = 5.7-7.0) and 8.2 (CI = 7.6-8.9) in 1960–1969 and 1970-

1979, respectively. In the 1980s and 1990s, this rate declined to 2.7 (CI = 2.4-3.1) and 0.5 (CI = 0.4–0.8), respectively (Figure 7A) [16]. Age at disease onset ranged from 11 to 68 years; the mean age of onset increased from 30.2 (CI = 27.5-33.0) to 37.1 (CI = 35.1-39.1) years from the 1950s to the height of the epidemic in 1970-1979 (Figure 7B). The female-to-male ratio changed from 2:1 during the 1950s and 1960s to approx. 1:1 in later decades (Figure 7C). The excess of female morbidity coincided with a higher proportion of acute/subacute VEM. Towards the end of the epidemic, acute VEM disappeared before subacute VEM; the number of chronic VEM cases also declined (Figure 7D).

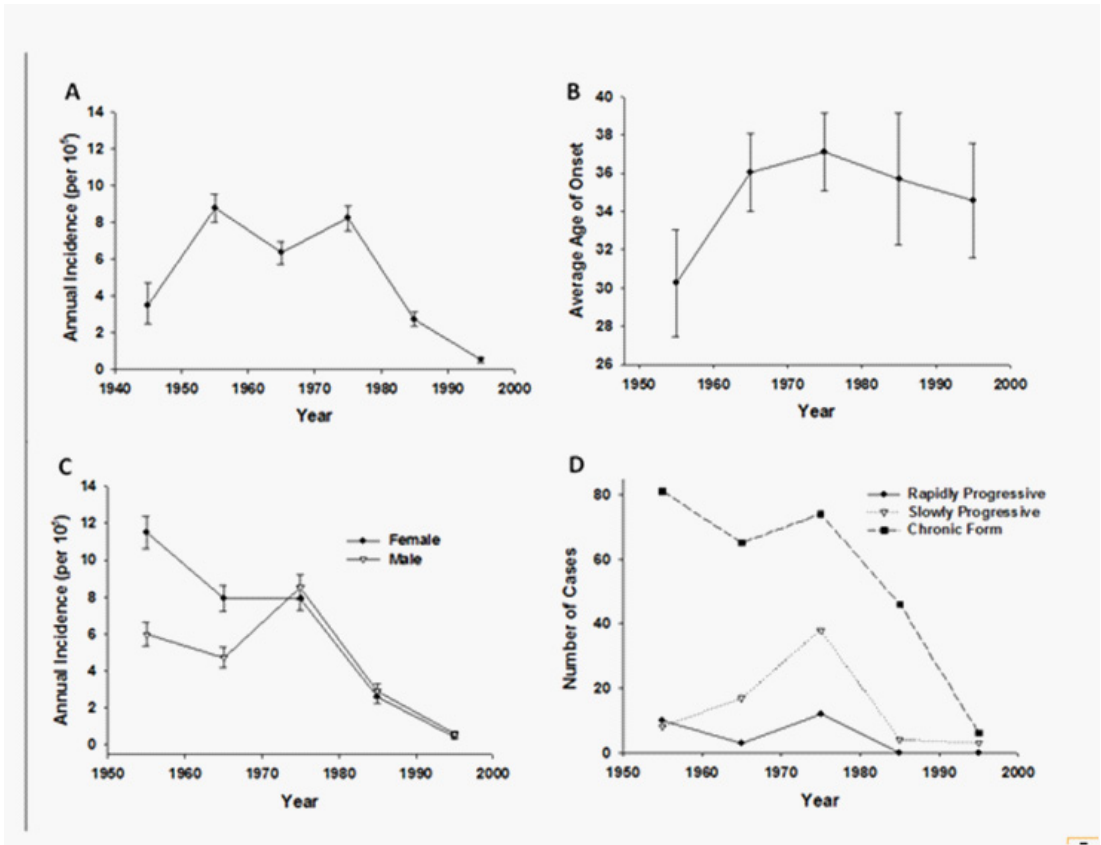


Figure 7: Multi-decade overview of the Viliuisk encephalomyelitis epidemic in Northeastern Siberia. A. Average annual incidence rate per 100,000 population. B. Average age of disease onset. C. Average annual incidence rate in males and females. D. Number of patients with various clinical forms of VEM. Vertical lines represent 95% CIs.

Trends in Territorial Spread

According to historical data, the first VEM cases were identified in small villages around Lake Mastakh (close to the Viliui river) between 1890 and 1925 [17]. Villages in the same geographic region were the epicenter during the 1940-1959 outbreak [2]. Additional cases were detected in these and progressively distant villages in the 1960s-1970s (Figure 8). Over time, the epidemic expanded southeast towards more densely populated industrial regions near the capital city of Yakutsk. The overall number of villages having new cases of VEM grew from 4 in 1940-1949 to 31 in 1950-1959 to 44 in 1960-1969, and to 51 in 1970-1979 (Figure 8). The affected territory increased 15-fold over the course of the epidemic and the geographic center of the affected area moved 94 km away from Lake Mastakh in 1940-1949, 142 km in 1950-1959, and 262 km in the 1960s-1980s (Figure 9). Villages with patients newly registered in 1980-1989 and 1990-1999, during the decline of the VEM epidemic were closer to the epicenter on Lake Mastakh (Figures 8 and 9) [16].

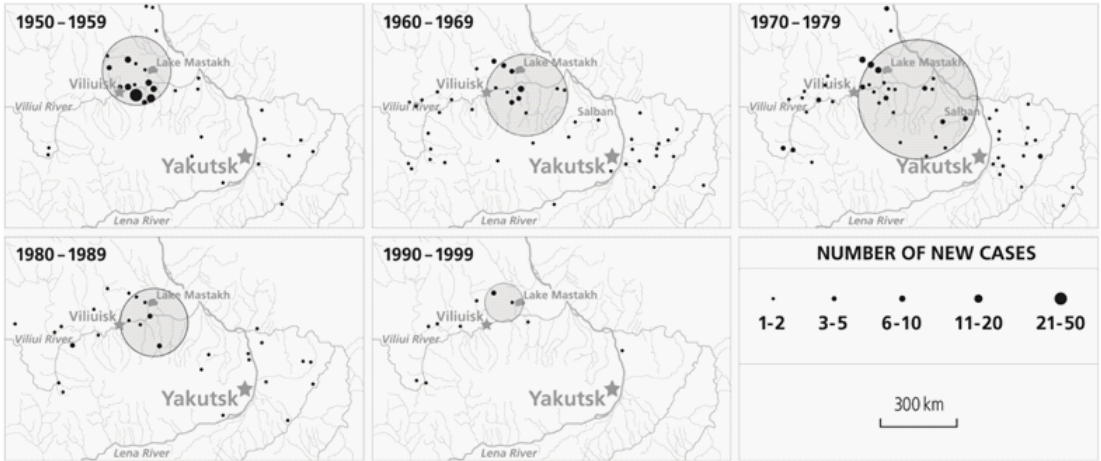


Figure 8: Location of villages in which new patients with Viliuisk encephalomyelitis were identified from 1950-1999. The 1940-1949 interval is represented by surviving patients who were diagnosed and registered in 1951.

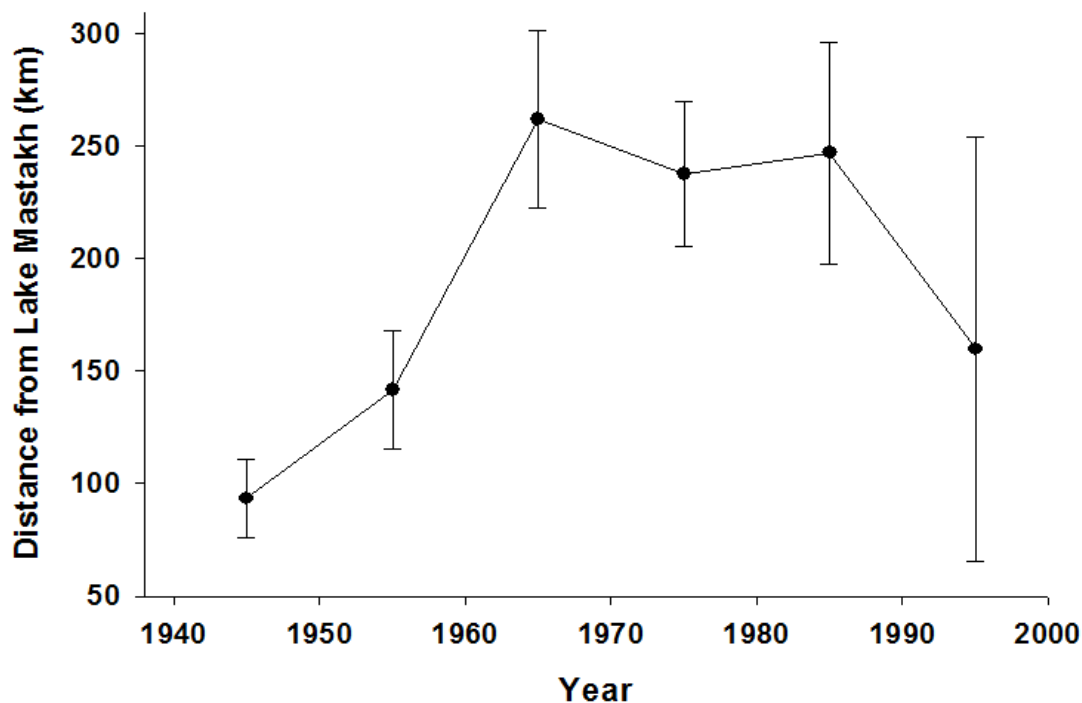


Figure 9: Distance (km) between the geographic center of the initial Viliuisk encephalomyelitis outbreak (Lake Mastakh) and villages in which new VEM cases appeared in subsequent decades. Vertical lines represent 95% CIs.

Patterns of Intra-familial VEM Transmission

Multiple cases of VEM in the same household were observed more frequently than expected by chance; of 1,090 households studied in six mid-Viliui villages, 33 (3%) households had a solitary VEM patient whereas 15 (1.4%) households had two or more VEM patients, greater than expected given the average VEM prevalence of 1.6% at the time of the study ($P < 0.0001$) [18]. Numerous observations of disease occurrence in non-genetic relatives as a result of residential exposure indicate an environmental rather than a genetic risk factor. Typically, a household member contracted VEM after prolonged cohabitation with an already ill family member [19]. The spread of VEM into more densely populated and developed regions occurred through massive migration. Analysis of four newly affected villages established a chain of cases that started with immigrants from high-risk areas and involved local residents who never left their home villages [6].

Search for the Pathogen

To identify the putative VEM agent, Sarmanova and colleagues inoculated clinical materials (brain tissue, CSF, blood, nasopharyngeal washings, and feces) from patients with acute, subacute

and chronic VEM into experimental white mice; eleven viral isolates were obtained [20]. These “Viliuisk virus” isolates cross-reacted strongly in complement-fixation tests with all known strains of the Theiler’s Murine Encephalomyelitis Virus (**TMEV**) and weakly with Encephalomyocarditis Virus (**EMCV**) strains [21]. To determine whether “Viliuisk virus” is a human pathogen or a murine contaminant, viral genomes were sequenced; nucleotide sequence differences were found between the “Viliuisk virus” and representatives of the TMEV group [22], indicating that Viliuisk Human Encephalomyelitis Virus (**VHEV**) is a separate Theilovirus clade [23]. However, its etiological significance is undetermined because not all VEM patients produce neutralizing antibodies against this virus [24].

Another candidate VEM agent was isolated following co-cultivation of explanted brain cells from a VEM patient with cultured cells, resulting in the isolation of the “KPN agent”, named after the patient’s initials [25]. This agent reacted in an indirect immunofluorescence assay with sera from VEM patients, indicating its potential involvement in VEM. Further characterization of the KPN agent showed that it contained DNA, RNA, and ribosomes prior to its identification as *Acanthamoeba castellanii* [26]. This research project was suspended because of unsuccessful additional attempts to re-isolate this pathogen from VEM patients [27].

A large-scale serological approach was also taken to find indirect evidence of pathogen exposure. Serological screening of 61 VEM sera for 46 known infectious agents, including protozoa, viruses and rickettsia, was carried out from 1991-1996 [24]. Although there were no positive leads, this study excluded a large number of candidate agents, helping to focus ongoing pathogen discovery efforts.

CONCLUSION

VEM is an enigmatic neurological disorder of likely infectious etiology that reached epidemic proportions in the geographically isolated Sakha people. Multi-decade studies of clinical, neuropathological, and epidemiological data indicate that VEM is a unique disease entity with a substantial immunological component. Despite comprehensive clinical studies and experimental investigations, the cause of VEM remains elusive.

VEM is a complex disease with three clinical variants that can be distinguished based on their rate of disease progression. Acute VEM results in substantial neurological damage and death within a year of disease onset. If not fatal within the first year of illness, subacute VEM is notable for brief clinical remission followed by gradual neurological decline with dementia, dysarthria, and marked spasticity. Chronic VEM is similar to prolonged subacute VEM and is separated by the duration of disease (> 6 years).

Neuropathological examination and CSF analyses indicate that VEM has a strong inflammatory component with lesional, cell count, and total protein concentration changes that mirror disease progression. Intrathecal production of oligoclonal IgG, persisting for over three decades after disease onset, also supports an immune-based pathomechanism. In prolonged disease, fibrotic

meninges and adhesions impede CSF circulation, resulting in increased intraventricular pressure, hydrocephalus, and brain atrophy.

Clinical and epidemiological studies indicate that VEM is caused by an environmental agent. Although mostly a disease of ethnic Sakha, its occurrence in ethnic Evenk and individuals born from mixed marriages argues against primary genetic causation. Although data are limited, VEM is more likely to occur in summer months (May-August), coinciding with outdoor preparatory activities, such as hunting, fishing and pasturing of cattle, through which an environmental agent could be readily encountered. However, this is also the time of year when people are most likely to receive medical attention. In the early epidemic, acute VEM affected younger adults, with a predilection for women; however, it is unclear what behavior would account for this pattern. Later in the epidemic, the increase in disease duration was likely due in part to improved patient care and extensive therapeutic interventions in early stage disease, thereby reducing mortality from complications.

Aggregation of cases in households and small villages indicates that VEM is a transmissible disease that can spread geographically. In households with two or more VEM patients, long-term cohabitation with an affected individual was a notable risk factor for disease. Family members were not always genetic relatives because the Sakha have a long-standing tradition of adopting young, old, and chronically sick community members to improve their chances of surviving harsh climactic conditions. The geographic spread of VEM coincided with documented massive migration. Starting in the mid-1950s, resettlement was allowed and sponsored by the Soviet Government to promote rapid development of newly discovered mineral resources. Most known migrant patients came from high-incidence VEM regions during the 1950s, 1960s, and 1970s; data from four newly affected villages established a chain of cases that started with immigrants from high-risk areas and involved local residents who never left their home villages. That people living in larger and more developed villages were affected with VEM indicates that an environmental agent, such as a parasite or a vector, accompanied the migrating Viliui population. The decline of the epidemic is attributed to the isolation of patients with acute and subacute VEM in the 1980s and 1990s in dedicated hospitals and other facilities. Persistence of the disease in the Viliui region may reflect more “stable VEM foci” with easier human-to-human or animal-to-human transmission due to cultural traditions, economic circumstances or natural environments.

Despite numerous classical and molecular attempts to isolate a VEM pathogen, the cause of this disease remains elusive. Isolation of VHEV, a novel Theilovirus, is intriguing because related members of the Cardiovirus family cause persistent CNS infection in mice and other Theiloviruses (Saffold 1, 2, and 3) cause polio-like flaccid paralysis and acute encephalitis in humans [28, 29]. Isolation of *Acanthamoeba castellanii* is also intriguing because it is found in fresh lake water, soil, and waste water, causes encephalitis when inoculated into experimental mice and rhesus macaques, and also causes primary amoebic meningoencephalitis in immunocompromised humans.

Although the etiology, mode of transmission, and pathomechanism(s) of VEM remain obscure, multi-decade clinical and experimental data indicate that VEM is a transmissible disease that broke through its confines in a geographically isolated indigenous population to produce an epidemic of severe neurological disease in a larger and more densely populated area of central Sakha (Yakutia). Although now in decline, molecular approaches to identify the cause and/or delineate the pathomechanism(s) of VEM are ongoing using banked clinical materials. Discovery of the putative VEM agent is the key to understanding and treating this disease and is paramount in case of re-emergence as economic development brings the Sakha (Yakut) Republic closer to the rest of the industrialized world.

ACKNOWLEDGEMENT

NMR was funded through a SEAMO New Clinician-Scientist Investigator Award and the Queen's University Principal's Development Fund. GLG was supported in part by the Intramural Research Programs of the National Institute of Neurological Disorders and Stroke. PFA and VAV were funded by the Ministry of Education and Science of the Russian Federation, project 1742.

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