

Viliuisk encephalomyelitis in Eastern Siberia – analysis of 390 cases

In memory of D. Carleton Gajdusek

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Folia Neuropathol 2009; 47 (2): 171-181

Foreword

Professor D.C. Gajdusek is famously known as an outstanding investigator of subacute and chronic neurological disorders occurring in indigenous populations of various regions of the world, primarily in the Pacific. He viewed the work on Viliuisk encephalomyelitis (VE), a fatal disease prevalent in some regions of Eastern Siberia, as a continuation of his life-long mission of discovering and characterizing rare diseases in little-known remote populations such as kuru, amyotrophic lateral sclerosis/parkinsonism dementia on Guam, and tropical spastic paraparesis in the Pacific and South America. Dr. Gajdusek visited VE endemic areas no less than 10 times between 1979 and 2004, and at each visit spent weeks traveling through the affected villages while conducting clinical and epidemiologic studies. In his multiple meetings with the President of the Yakut (Sakha) Republic and other officials he stressed the necessity of further detailed analysis of the problem, offering his ideas on how to proceed with the studies. In his latest letter to the President (2004) Dr. Gajdusek stated, among other things, "Viliuisk encephalomyelitis happens to be a very hard problem to solve. We remember a large epidemic of this disease in the 1950s, mainly in the Viliuisk region, described very clearly by Professor PA Petrov. Acute Viliuisk encephalomyelitis cases were later observed in many other regions. And we know that Viliuisk encephalomyelitis has not disappeared today...". This article is a summary of the current status of the VE epidemic.

Abstract

Viliuisk encephalomyelitis (VE) is a unique disease occurring in the Yakut (Sakha) population of Eastern Siberia. VE 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 neuropathologically by multiple widespread micronecrotic foci with marked inflammatory reactions and subsequent gliosis throughout the cerebral cortex, basal ganglia, cerebellum and brain stem. The acute febrile onset with cerebrospinal fluid pleocytosis and increased protein and neuropathology showing inflammatory reactions suggest that VE is an infectious disease, but the causative agent has not been identified. Initially detected in a small mixed Yakut-Evenk population of the mid-Vilui region, the disease subsequently spread south to densely popu-

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lated areas around the capital city of Yakutsk. The occurrence of secondary VE cases in households and the introduction of the disease by migrants into new 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.

Key words: Viliuisk encephalomyelitis, Yakut (Sakha) Republic, Eastern Siberia, Viliui River, inflammatory brain syndrome.

Introduction

Richard Maak, a Russian geographer and ethnologist, was the first to become aware of an unusual “weakening” (paralyzing) disease in a small rural population of about 4500 Yakuts living on the left bank of the middle reaches of the Viliui River [19]. Medical characterization of the disorder was originally made by a medical team from the USSR Ministry of Health conducting an epidemiological survey of the Viliui region in 1925-1926 [16]. Dr. Kolpakova provided a brief description of a chronic neurological syndrome in 16 patients with disease onset in 1891-1925. Systematic studies, documentation and registration of VE patients were initiated in 1951 by the Neurology Department of the Viliuisk Regional Hospital. Dr. Prokopii Andreevich Petrov was in charge of the Department between 1951 and 1958. His work on what was later termed as an outbreak of VE in the Viliui region [23, 24] has become the first fundamental study on the subject. The disease later appeared in neighboring districts and eventually reached more densely populated regions of the Yakut Republic. On realization that VE was spreading to previously unaffected geographic regions, a much better equipped research center was established in the 1960s in the Republican Hospital of the capital city of Yakutsk. This second center working for many years under the leadership of Dr. Afanasii Ivanovich Vladimirtsev took over surveillance and hospitalization of VE patients in the entire Yakut Republic [33].

Studies of VE attracted scientists from several outside research institutions who accumulated a vast amount of data. Multi-year detailed research was conducted by the Moscow Institute of Neurology and St. Petersburg State Medical Academy [25,30,31], Moscow Institute of Poliomyelitis and Viral Encephalitis [6,11,13,28,29,35], and the American National Institutes of Health [9,12,20]. Published and non-published materials accumulated by these institutions were available for this analysis.

Isolation of the causative agent from patients’ brain tissue and CSF has been repeatedly attempted.

V-1 strain of “Viliuisk virus” isolated by intracerebral inoculation of mice with brain tissue from a VE patient [25,26,27] was shown to cross-reacts with Theiler’s murine encephalomyelitis virus (TMEV) and weakly with encephalomyocarditis virus [4] – both members of the *Cardiovirus* genus, *Picornaviridae* family. TMEV is a natural mouse pathogen that causes a persistent CNS infection in mice, leading to immune-mediated demyelination [17]. Based on comparative studies, Viliuisk virus appears to be a highly divergent strain of TMEV and possibly a separate clade of Theilovirus [32]. Recent discoveries of Theiloviruses causing human disease [1,15] may indicate that the Viliuisk virus is a TMEV recombinant circulating in humans [18] or between humans and animals. Another candidate agent (KPN) was isolated by inoculating MIO and DKCh cell lines and subsequently identified as *Acanthamoeba castellanii* [5], but no further isolations were reported. Recent attempts at inoculating a wider range of laboratory animals have also failed to discover the pathogen (D.C. Gajdusek, R.M. Garruto, personal communications).

Materials and Methods

Study population

The vast, sparsely populated territory of the Yakut (Sakha) Republic is located in northeastern Siberia, known as the coldest area in the Northern hemisphere with average January temperatures of -50°C and a world record of -72.2°C . Yakutia is abundantly rich in raw materials; diamond, gold and tin ore mining industries are the major focus of the economy. The Yakut (Sakha) population originated from a nomadic Central Asian tribe that migrated to the North-Siberian plains 600 to 900 years ago under the pressure of Mongol expansion. The newcomers brought to Siberia a dialect of Turkic language and cattle/horse breeding culture [21]. By the time of Russian colonization at the beginning of the 17th

century the Yakut people still lived in a relatively small area in the Lena-Aldan valley (currently Central Yakutia). The land around these Yakut settlements was occupied by Evenks and Evens, reindeer herders and hunters [22]. Being a more civilized and powerful population with a developed economy less dependent on severe climatic conditions, the Yakuts assimilated the indigenous populations [7]. Remnants of Evenk tribes can still be found in the northern parts of Viliui valley. The population grew significantly within the past 3 centuries, reaching 432,290 in 2002. The rural population of 339,281 consists almost entirely of Yakuts.

A traditional rural Yakut household would include representatives of several generations, with more than a single married couple and an average of 5.5 children [8]. Moreover, because of harsh conditions it has become highly ethical to adopt for lengthy periods of time the villagers who are unable to care for themselves – orphans, elderly and the sick, either related or non-related to the host family. The Tsarist and Soviet Governments restricted movements of people by controlling inter-regional migration; only after World War II, when the development of Siberian resources significantly intensified, was the local population allowed to migrate to centrally located industrial centers and regions more favorable for agricultural development. Within the past several decades about 11% of the rural population has migrated into better developed urban regions [8].

The population of the middle reaches of the Viliui River is in many respects different from other Yakut populations as the Viliui Yakuts were generally more liberal toward the local Evenk tribes and more readily assimilated with them. Most VE cases were originally found in a small mixed Yakut-Evenk population in villages around Lake Mastakh that is well known to investigators as the supreme VE endemic area.

VE ascertainment

Patients suspected of VE were systematically identified, studied and documented for more than five decades beginning in the early 1950s. Early detection and frequent follow-ups were accomplished by village-to-village searches and periodic hospitalizations. Patients in the acute phase of illness remained in the VE Research Center for the entire duration of illness. Patients with protracted illnesses were returning for follow-ups at least once a year. Patients with chronic

VE were hosted for life in a specialized nursing facility with 50-bed capacity located in the suburbs of Viliuisk. All cases underwent standardized neurological assessment. Neuropathological studies have been conducted by three independent groups [3,20,29]. Traveling teams of neurologists and epidemiologists periodically visited every affected village for follow-ups and detection of new patients.

Of more than 1000 fully studied patients with disease onsets between 1940 and 1999, 390 met diagnostic criteria for definite VE based on clinical, pathological, laboratory and epidemiologic data and documented in a Registry. Date and place of birth, ethnicity, the exact or approximate (up to a week) date of disease onset, the location where the patient lived at the time of disease onset, family structure, history of travel, and the date of death were established in each case. A four-page clinical chart describing symptoms of the acute and chronic phases of illness and results of laboratory, imaging and neuropathological studies were attached to the Registry entry. The overall number of patients studied pathologically was 36 (9% of all patients in the Registry). The Registry was computerized in 1999.

Studies were performed under clinical protocols approved by the Institutional Review Boards of the Yakut (Sakha) Institute of Health and the U.S. National Institutes of Health.

Results

Clinical features

VE is a progressive meningoencephalitis that starts acutely with severe encephalitis and meningism lasting several weeks to several months; some patients die within the acute phase, while survivors develop a slowly progressing neurological syndrome characterized by dementia, dysarthria, spasticity, muscle rigidity, postural or kinetic tremor, and cerebrospinal fluid (CSF) pleocytosis lasting with intermissions up to 6 years. In some patients, the disease stabilizes in an advanced phase and they remain in a steady state of global dementia and severe spasticity for 20 years or longer. The age of disease onset varied between 11 and 68 years with an average of 30.2 (95% CI 27.5-33.0) at the beginning of the epidemic that increased in the later decades to 37.1 (95% CI 35.1-39.1) years. The female-to-male ratio has changed from a 2 : 1 female excess during the time when the acute VE was a frequent form (the

Table I. Clinical/pathological features of VE in patients with the duration of illness 12 months or less

Features	Patients														
	ME	VV	BO	IA	KA	KM	PA	IS	BS	DM	AE	SP	EA	PA	OT
Gender (Female/Male)	M	F	F	F	M	F	F	F	M	F	F	M	F	F	F
Age at onset (years)	43	38	45	49	33	18	53	61	59	38	37	18	36	47	46
Duration of illness (months)	2	2	3	4	4	4	5	5	6	7	9	11	11	12	12
max temperature °C	40.5	39	40	39	40	40	39	40	40	39	38	38	40	39	41
coma	+	++	++	+	+	+	+	+	+	++	-	+	+	++	+
neck rigidity and Kernig's sign	+	+	+	+	+	+	+	+	+	+	+	++	++	+	+
relapse of febrile illness	-	+	-	-	+	-	-	-	-	+	-	-	-	-	+
death in comatose state	+	+	+	+	-	-	-	+	-	+	-	-	+	-	-
cognitive decline	c	c	c	c	+	+	++	c	+	c	+	+	c	+	+
dysarthria	c	c	c	c	+	+	-	-?	+?	+?	+	+	++	++	+
dysphagia	-	-	+	+	+?	+	-	-	-	+	-	-	-	+	-
increased deep tendon reflexes	+	-	+	+	+	+	+	+	+	+	+	++	+	+	+
spastic tetra- paraparesis	c	c	c	c	++	+	-	c	-	+	+	+	++	++	+
increased muscle tone	+	+	+	+	++	+	+	+	+	+	+	+	+	+	+
Babinski sign	+	+	+	+	+	-	+	+	+	+	-	+	-	+	+
spastic gait	c	+	++	c	+	+	+	c	+	c	+	+	+	+	+
sphincter dysfunction	+	+	+	+	-	+	+	+	-	-	+	+	+	+	+
lower motor neuron signs	-		-	-		+	+	-	-	+	-	-	-	-	
cerebellar ataxia	c	-	-	+	-	+	-	+	-	-	+	+	-	+	+
sensory deficits	c	c	-	-	-	-	pro	-	-	-	-	-	+?	-	-
Imaging: brain atrophy	-	-	-	-	+	-	-	-	+	++	+	+	++	+	++
CSF cell count (per mm ³)	45	8	44	55	167	66	27	7	27	10	78	12	16	32	70
predominant cell type	lym		lym	lym	lym	lym	lym				lym			lym	lym
CSF protein (mg/dL)	33	166	99	330	99	?	66	66	99	264	132	33	132	66	99
Postmortem examination: micronecrotic foci	+	+	+	+	+	+	nd	+	nd	nd	nd	nd	nd	+	nd
Postmortem examination: infiltrates	+	+	+	+	+	+	nd	+	nd	nd	nd	nd	nd	+	nd

The sign is expressed + moderately, ++ strongly, - not expressed; c - not assessed because of coma; +? or -? - indefinite response, result unknown; lym - lymphocytes; pro - proprioceptive sensation decreased; nd - autopsy not performed.

1950s and 1960s) to comparable rates in males and females in the later time intervals. Mean duration of illness was 17.8 years, varying from 2 months to 34 years. Three hundred and thirty-eight patients (87%) have died by the time of this analysis. Presenting

signs and symptoms of VE include fever in 62% of patients, headache, vomiting, muscle aches, altered mental status, fatigue, nausea, back pain, and stiff neck. Further clinical course, according to its speed of evolution, may be divided into three types of illness:

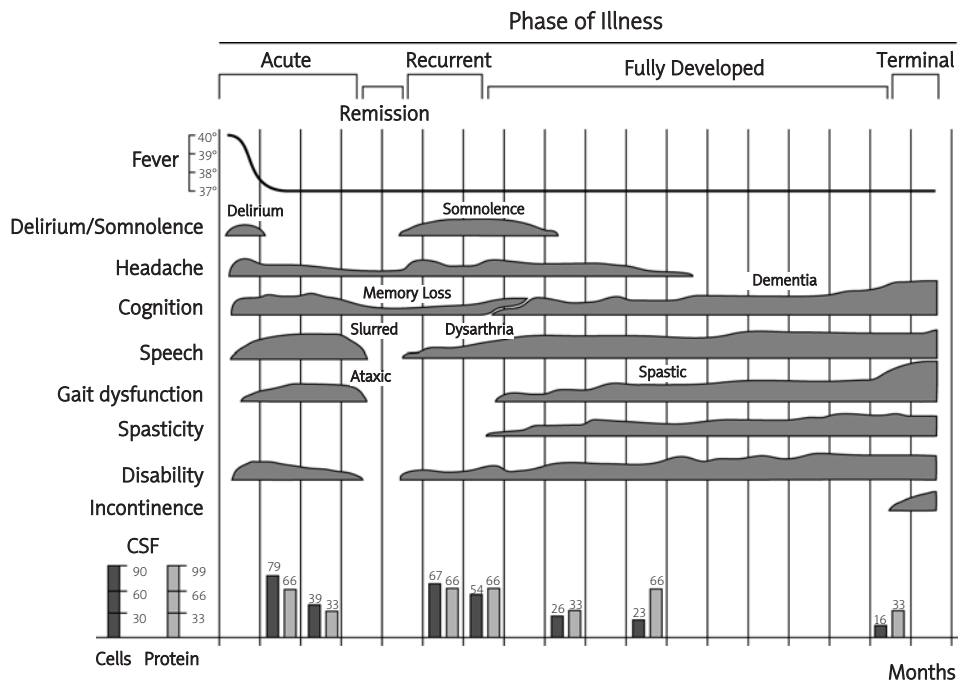


Fig. 1. Clinical chart of a patient with slowly progressive variant of Viliuisk encephalomyelitis. The patient was admitted with delirium, fever, chills, headache, myalgia, nausea and frequent vomiting at the age of 38 years. He remained mentally and physically slow, shaky and showed neck muscle stiffness and Kernig's sign. At the end of the tenth week he recovered enough to return to work. But after several weeks of relative stability his speech became slurred, he experienced memory lapses, had hyperactive deep tendon reflexes, bilateral Babinski sign, decreased muscle strength predominantly in distal lower limb muscles, and markedly spastic gait. Within several months, the patient's cognitive abilities further declined, his speech became severely dysarthric and he could walk with great difficulty due to spastic quadriparesis. Sphincter dysfunction was another feature. The disease relentlessly progressed thereafter, and he died 17 months after the onset of illness. WBC count in the CSF was consistently abnormal during the entire course of illness.

(i) rapidly progressive (acute/subacute), (ii) slowly progressive and (iii) chronic.

Rapidly progressive variant – this most ominous variant was observed in 19 patients; 15 of them who died within 12 months from the disease onset are characterized in Table 1. There was sudden onset of chills, fever and headache that quickly became excruciating. All patients were comatose at presentation and remained in a state of diminished level of awareness for days or weeks. All had fever that persisted 2-6 weeks, then subsided and in some cases remained at a low-grade level for several months. Headache remained intense for several weeks. Chills, muscle and joint pains, paraesthesias with a sensation of vibration or electrical current in the extremities and pain along the nerve trunks were common. Stiffness of the neck muscles and Kernig's sign were seen in each case (Table 1). Signs of cranial nerve

dysfunction, including ptosis, diplopia, strabismus, impaired convergence and accommodation, were frequent findings. Cognitive decline was evident soon after the patients came out of coma. Bradykinesia, muscle rigidity, and dysarthria appeared between the second and fourth weeks after onset; hyperactive deep reflexes and spastic quadriparesis developed at about the same time or later in the course of illness. The disease was relentlessly progressive with no remissions; all patients died within 2-24 months.

Slowly progressive variant was observed in 65 patients. It had a characteristic sequence of phases: acute, recurrent-exacerbative, fully developed, and terminal (a clinical chart of a typical patient is presented in Fig. 1). There was a sudden acute onset similar to that observed in the rapidly progressive forms, followed by muscle stiffness and ataxia, difficulty with speech, and mental disorientation.

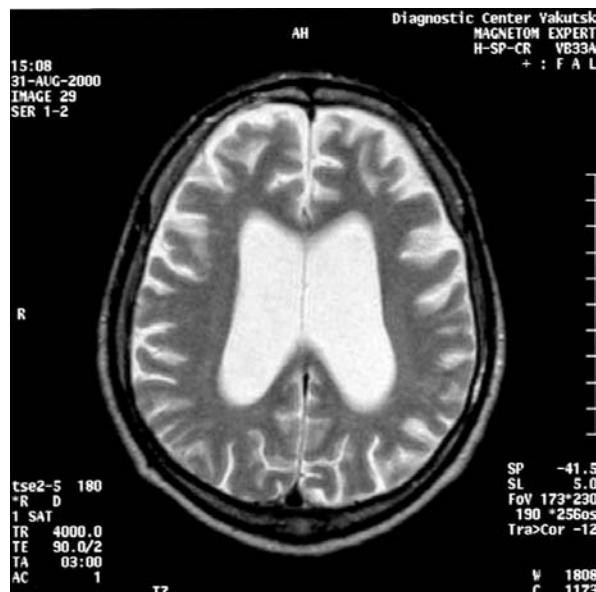


Fig. 2. Brain magnetic resonance image of a 38-year-old patient with slowly progressive Viliuisk encephalomyelitis, 12 months after disease onset. Prominent diffuse cerebral atrophy.

With subsiding temperature and headaches, some patients tried to return to work, but most could not handle it well. Behavioral changes, including loss of interest, apathy and somnolence, persisted. After varying periods of partial remission, from several weeks to 12 months, symptoms exacerbated and recurrent headache, stiffness, muscle weakness and pain in the extremities reappeared. A progressive syndrome characterized by dementia, characteristic dysarthric speech, pyramidal quadri- or lower paraparesis, and associated bradykinesia, clumsiness, postural instability and cogwheel rigidity, slowly developed. Ophthalmoplegia, dysphagia and choreiform movements were seen in some patients. Cerebellar symptoms were rare and no sensory deficits were observed. Muscle stiffness and spasticity steadily progressed until the patient was unable to walk. Some patients suffered hypothalamic involvement. Further down the line, patients became yet more profoundly disabled. They appeared mute, unable to communicate or walk, exhibited global dementia and were usually incontinent. Death occurred 24 to 72 months after disease onset from disease progression.

Chronic type of illness was similar to the slowly progressive type, but the patients stabilized in an advanced stage of illness and showed no further

progression. Some patients did not remember an acute episode at the onset and apparently developed a primary chronic disease. Death occurred from hypostatic pneumonia or renal insufficiency secondary to sphincteric problems or accidents, and some lived to be very old.

Laboratory findings. In patients with acute form, CSF showed inflammatory changes with moderately elevated protein concentration and pleocytosis of between 20 and 90 cells/mm³. Most of the cells were mononuclear. Modest pleocytosis persisted for many years through all the phases, declining slowly after the sixth year of illness. The protein concentration was moderately elevated to 70-165 mg/dl. In chronic disease, CSF did not show abnormal CSF changes. High-pressure hydrocephalus seen in the early stages was due to adherent leptomeningitis with subarachnoid obstruction [10]. Later in the course of the disease, diffuse brain atrophy and atrophic low-pressure hydrocephalus developed. Electroencephalographic recordings revealed a diffuse lowering of electric potentials, mainly in the frontal and parietal regions. Alpha rhythm was replaced by low-amplitude, irregular beta rhythm with superimposed polymorphic slow waves. Isoelectric focusing identified intrathecal IgG synthesis in the absolute majority of patients with clinically/pathologically verified VE, confirming that long-term persistent inflammation in the brain is part of VE pathogenesis. The inflammation is most active in the progressive phases of illness during which cellularity in the brain tissue is increased and the intrathecal production of IgG is most active. Imaging of the brain reveals marked diffuse cortical atrophy (Fig. 2).

Neuropathology

In cases in which the disease progression was rapid and death occurred within 6 months, postmortem examinations identified diffusely edematous cloudy meninges infiltrated with mononuclear, plasma and polymorphonuclear cells; inflammatory changes were especially pronounced in the meninges overlying the affected cortical areas [20]. In the brain parenchyma, multiple widespread micronecrotic foci consisting of eosinophilic condensed granular material 0.4 mm in diameter surrounded by inflammatory infiltrates were observed throughout the cerebral cortex, basal ganglia, cerebellum and brain stem, and were less frequently seen in the subcortical white matter (Fig. 3A). The inflammatory infiltrates were composed of lymphocytes (predominantly T-cells with occasional

B-cells), microglial cells, macrophages, and reactive astrocytes. Perivascular cuffs consisting of mononuclear cells were widespread in the affected cortical areas. Complete destruction of neurons in the affected areas and diffuse neuronal loss outside of these areas were found. Randomly scattered necrotic foci were present in all sections of the cortex. Cranial nerve nuclei were predominantly spared. The limited sampling of basal ganglia tissue available revealed foci within the putamen, caudatum, thalamus and hypothalamus. Spinal cord foci involved lateral grey matter and anterior and posterior horns. Other features in the cases with rapid progression included localized collections of parenchymal microglial cells and T lymphocytes and prominent diffuse meningeal and parenchymal perivascular chronic inflammatory cell infiltrates. Most of the lymphocytes seen either in the parenchyma or in a perivascular distribution were T-lymphocytes immunoreactive for CD45RO. Only occasional perivascular B lymphocytes, immunoreactive for CD19, and plasma cells were seen. Neutrophils, eosinophils or giant cells were not evident. The choroid plexus and ependyma were not affected. Intra-nuclear or cytoplasmic inclusions and neurophagia were not identified. Special stains for organisms were unrevealing. Electron microscopy did not disclose viral particles; however, the sections were of poor quality due to the method of extraction and post-fixation.

In slowly progressive cases, necrotic foci were less frequent but similar in character to those seen in the rapidly progressive cases. Other less active foci showed central lysis of tissue with adjacent reactive gliosis, T-lymphocytes and microglial cells (Fig. 3B). Small vessels within and adjacent to these foci showed prominent endothelial cells and perivascular cuffs of T-lymphocytes. The extent of active, organizing and lytic foci within the parenchyma varied case to case, some showing confluence of many lesions leading to extensive cortical destruction in all cortical laminae, reactive gliosis and secondary demyelination in underlying white matter. Perivascular inflammatory cells were seen in the thalamus, hypothalamus and caudate nucleus. Bergmann astrocytes were prominent in the folia adjacent to the organizing cerebellar lesions. Pathological overlap between the rapidly and slowly progressive cases is evident since active morphologically identical necrotic foci are seen in both categories. However, most of the observed foci are actively organizing or organized.

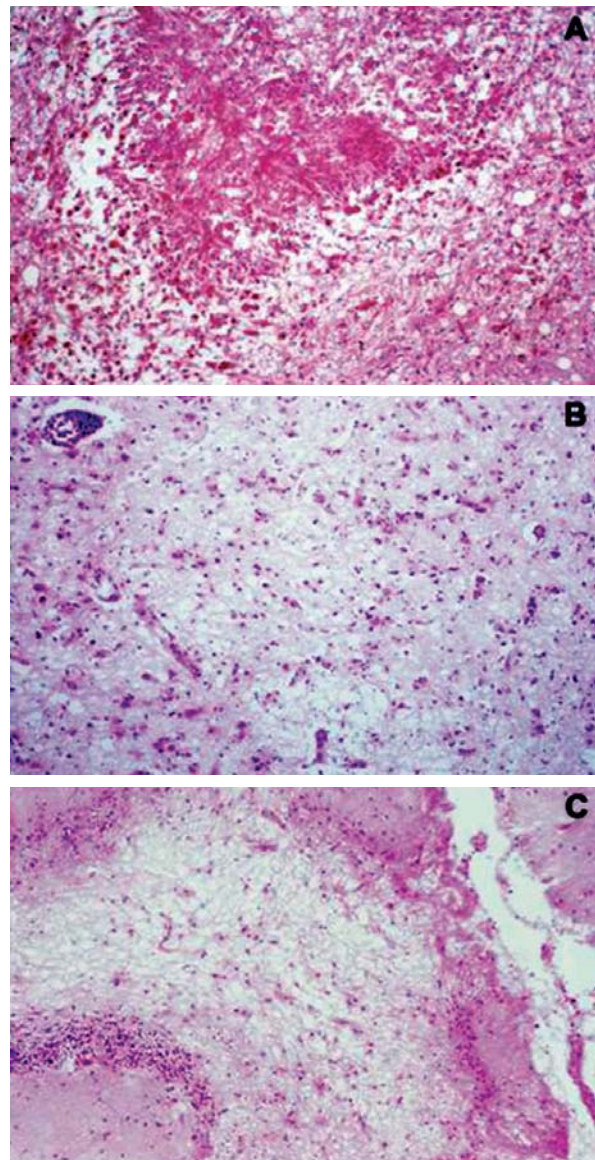


Fig. 3. (A) Rapidly progressive Viliuisk encephalomyelitis. Typical encephaloclastic focus showing central necrotic debris, palisaded by microglial cells, macrophages and lymphocytes. Hematoxylin and eosin. (B) Slowly progressive Viliuisk encephalomyelitis. Parenchymal and perivascular collections of lymphocytes and neuropil lysis, neuronal loss and reactive astrocytes within a focal area of the cerebral cortex. (C) Chronic Viliuisk encephalomyelitis. Focal area of lysis within the cerebral cortex showing central gliosis and some residual small vessels. There is minimal residual inflammation in the surrounding parenchyma. Original magnification in (A) 160 ×, in (B) 80 ×, in (C) 79 ×.

In the chronic “burnt out” cases, fibrotic adhesive meninges had minimal residual inflammation; atrophic cerebral cortex showed microcysts that replace micro-necrotic foci, with no active inflammation, rimmed by gliosis, present in a similar cortical distribution to the slowly progressive cases (Fig. 3C). The cortex appeared microcystic, atrophic and gliotic, with confluence of many lesions. There was severe neuronal loss. Occasional small glial scars were seen in deep grey matter, predominantly in the putamen. Scattered gliosed and lytic foci were seen in the basis pontis, pontine tegmentum, medulla and grey matter of spinal cord. Depigmentation of the substantia nigra was not evident. Perivascular T lymphocytes, reactive astrocytes and microglia were scant in the parenchyma and meninges.

Epidemiology

All patients were ethnic Yakuts, except for 6 who were Evenks and 11 who were born from Yakut-Evenk mixed marriages. A great number of VE cases had the onset of their illness in May, June, July or August (59.5% of 215 cases with known day/week of disease onset), which may be due to more intensive outdoor activities such as hunting, fishing and pasturing of cattle that subject people to frequent exposure to possible environmental factors provoking the onset of the disease. All registered VE patients were born and most of them lived their entire lives in small villages. VE patients have been identified in 110 villages with population sizes from 250 to 3,000 individuals in twelve administrative regions of the Yakut Republic.

Territorial spread. According to historic evidence, the first 16 VE cases with the disease onset between 1891 and 1925 were detected in several villages around Lake Mastakh [16]. Subsequently identified 1940-49 cases and the 1950-59 outbreak of VE occurred in this same area [23,24]. If this location is accepted as the site of the initial VE outbreak, the average distances to villages in which later VE cases occurred was increasing. There is a significant spatial separation between the territorial limits of the 1940-49 and 1970-79 case distributions (Figure 4) with the expansion of the epidemic towards the more densely populated and better developed areas to the south-west along the Viliui River and south-east toward the capital city of Yakutsk. Massive migration of people in these directions was registered in the post-World War II years; resettlement was allowed and sponsored by the Soviet Government to promote rapid development of newly discovered mineral resources. Doctors regarded VE as a new disease brought by people who came from the Viliui Valley [13]. Analysis of data related to VE incidence in 4 villages around the city of Yakutsk established a chain of cases that started with immigrants from high-risk areas and later involved local residents who never left their village [13,34]. In the village of Salban, a migrant worker developed VE twenty-one years after his resettlement from Viliui. His two local consecutive wives developed VE in the 1970s and two further cases were identified in other local villagers. In Keptin, another newly affected village in the same area, VE was initially identified in two women migrating from Viliui and subsequently in three local Yakuts.

Trends in VE incidence. The annual VE incidence rate in the mid-Viliui region was already at its highest

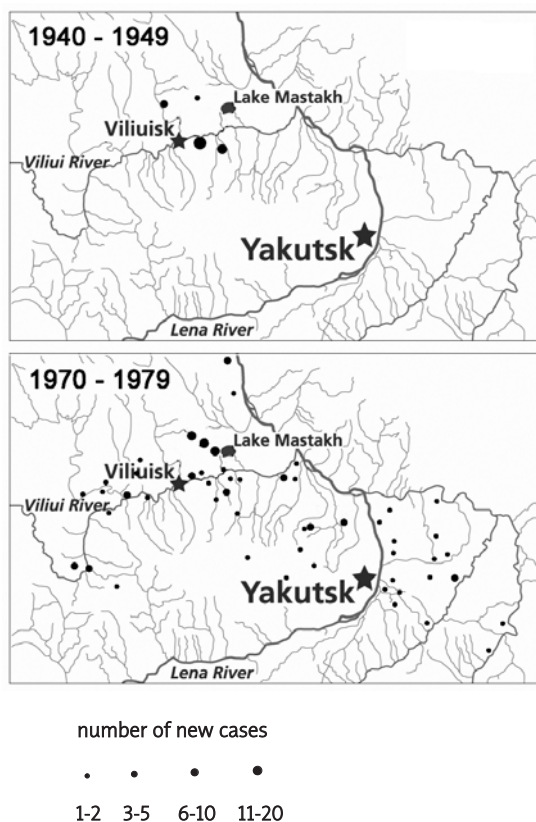


Fig. 4. Location of Yakut villages in which patients with Viliuisk encephalomyelitis were identified in 1940-49 or 1970-79. The territories affected in 1970-79 are located in more densely populated and better developed areas to the south-west along the Viliui River and the south-east toward Central Yakutia.

level of 103 per 100,000 when VE registry was initiated in the early 1950s; apparently, the epidemic started and even reached its peak in this region during the 1940s. In contrast, the incidence rate in the densely populated south-western villages grew from zero to 33.8 per 100,000 in the 1970s and decreased in the 1980s and 1990s (Fig. 5). The age of disease onset and incubation time increased, suggesting that the transmission slowed. The shifts in incidence rates, average age of disease onset and female-to-male ratio over the course of the epidemic are significant and apparently related to the pathogenesis of this disease and changing environmental factors.

Discussion

A 50-year study based on the largest known number of diagnostically definite VE cases allowed the clinical and neuropathological characteristics of VE to be refined and VE to be established as a unique disease. VE is a slowly developing meningoencephalitis with overt inflammatory responses in the brain. The presence in the CSF of restricted IgG oligoclonal bands is consistent with the conclusion that VE is primarily an inflammatory brain disease [14]. The VE incidence rate at the height of the epidemic reached levels equal to or higher than those for many common neurological disorders such as amyotrophic lateral sclerosis (ALS), hereditary ataxias, spastic paraplegias or neuropathies, and slightly lower than multiple sclerosis (MS). The disease affects predominantly young adults and in the first phase of the epidemic young women were affected twice as often as men, similar to the ratio seen in MS [2]. This changed in the later years when chronic VE became the predominant clinical type of illness.

Aggregation of VE cases in households and small villages indicates that VE represents a transmissible disease, although the causative agent has not yet been identified. Analysis of the territorial distribution of VE identified the Lake Mastakh-mid-Viliui region as the original source of the VE epidemic. Within the next three decades, the disease spread to the neighboring regions and later to distant localities in a general direction toward more populated territories of the Yakut Republic around the capital city of Yakutsk, with many new cases occurring in the local population. The fact that the population living in larger and economically better developed villages of

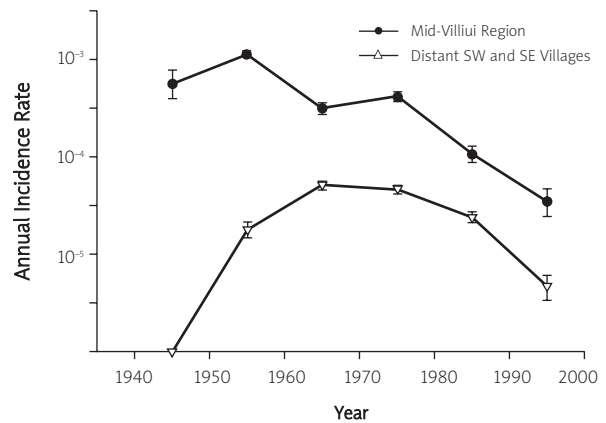


Fig. 5. Average annual incidence rates of Viliuisk encephalomyelitis during the epidemic in the Viliui region (filled circles) and the central region around the city of Yakutsk. Vertical lines correspond to 95% confidence intervals.

the central part of the Republic became affected with VE indicates that the environmental agent(s) were carried with the migrating mid-Viliui population. The recent retraction of the disease back to mid-Viliui areas signals that the Viliui region has more “stable VE foci” with perhaps easier human-to-human or animal-to-human transmission due to cultural traditions, economic circumstances or natural environments.

Significant social and demographic changes that occurred in the country within the past 25 years, and efforts at isolating patients with acute and slowly progressing forms of VE in specialized hospitals and a nursing home, led to a slow decline of disease incidence in the 1980s and 1990s. Kolpakova [16] and later Petrov [24] described unimaginable sanitary conditions in the Viliui region, unfit houses with high occupancy, no electricity, subsistent low quality food, non-regulated water supply, and no washing facilities. Communities were taking care of the disabled VE patients by putting them into related or unrelated local families for an unspecified period (at least for a winter). All these social factors promoted the spread of infection. In the 1960s, the Government subsidized a nursing home for patients who were denied further care by the villagers. In addition, extraordinary attempts were made to detect and diagnose VE cases early in the acute phase and hospitalize them for a long time in one of the two hospitals, thus isolating

the patient during the time they were likely to be contagious. There has been a very noticeable overall improvement in living conditions within the last 25 years. The privatization of farms reduced work-related contacts between villagers as compared to collective farms when each member, including VE patients in early phases of illness, was obliged to live for extended periods of time in camps far from home.

Although the etiology of VE, its origin and exact mechanisms of transmission remain obscure, the data presented in this communication demonstrate how a previously unknown disease that was endemic in a small indigenous population reached densely populated areas and produced an epidemic involving hundreds of victims.

Acknowledgements

The authors are grateful to the patients and members of their families for participation in the study. This research was supported in part by the Intramural Research Program of the National Institute of Neurological Disorders and Stroke, National Institutes of Health.

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