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Vliuysky encephalomyelitis: clinical polymorphism, focusing on slowly progredient fatal disease course. Variations of the epidemic process

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Summary

The introduction of clinical and epidemiological monitoring of different degree of reliability of the diagnosis of the Vilyuisk encephalomyelitis (VEM) risk groups of patients in the foci of disease, because of the still not confirmed data on suspected viral etiology of the disease, lead to polar points of view on the nature and pathogenesis of VEM. It is shown that the identification of long-term stable and remittent types of the clinical course of sub-acute and chronic VEM with exacerbations, leading to rapid fatalities, indirectly brings VEM with slow infections. It is suggested that the epidemic process of VEM varies dramatically by the prevalence of the mild polymorphous clinical forms above those authentic typical in some its periods.

***Keywords*:** Viliuysk encephalomyelitis, epidemic process, clinical and epidemic monitoring, sub-acute VEM, slow VEM, slow infection, clinical polymorphism.

Abbreviations: DPF – dementic-paretical form; SPF - spastic-pareticcal form; PSF - psychotic form; TVE - Torpid Viliuysk encephalomyelitis; ONMS - Organic neurological micro symptoms; MFP - slowly and fatally (malignant) progressive type of VEM; GLP - gradually, the long-term upward (benign) progredient type of current, TE - Torpid encephalopathy, VH - virus herpes, TBE – Tick borne encephalitis, PFTBE - progressive forms of TBE; PFVEM - progressive forms of VEM; ALS -amyotrophic lateral sclerosis.

Introduction

In connection with failures to isolate the causative agent of the Vilyuisk encephalomyelitis (VEM) most credible cases of disease by a special Commission of scientists of the Institute of poliomyelitis and virus encephalitis of AMS of the USSR in 1971, were adopted so-called nuclear clinical forms VEM in the form of dementia, dysarthria and spastic tetraparesis with the rigidity [5]. These irreversible manifestations of the disease were more often developed in patients surviving acute

prolonged febrile meningo encephalitic stage of the disease. However, from the 1950s - 60s, under VEM dispensary supervision sometimes were included people who get the lighter acute neuroinfections unclear etiology. Moreover, already in the 1950s, in the foci of VEM were registered practically healthy people with organic neurological microsymptoms (ONMS) that were initially taken for the residual effects migrated acute outpatient (or easily expressed mild) forms of the encephalitis. In the subsequent history of the disease in many patients VEM not excluded the presence of such encephalopathy states long before the disease, which in some cases was confirmed by clinical observations. It was ascertained, that the part of such people is gradually developing clinical picture spastic encephalopathy, border clinical manifestations with moderately severe clinical forms of chronic VEM [1].

Clinical and epidemiological studies L.G. Goldfarb and co-authors [5,11] with high probability demonstrated the possibility of horizontal transmission VEM from person to person. On prolonged incubation period of VEM (in average 17 years) is close to the slow infections. Negative results of various virological studies at VEM do not stop the attempts of some researchers to continue the study of such candidates to the etiology of VEM, as viruses Saffold and Taylor [9,10,12]. The discovery of the virus Saffold and its pathogenicity for humans increases the likelihood that Viliuysky virus could still be isolated from VEM patients and perhaps recombined in a collision with a population of Taylor murine encephalomyelitis virus. G.G. Karganova [8] currently continuing her work to the agent, dedicated E.S. Sarmanova [9,10].

Pathological findings in VEM [13], indirectly characterize lesions in brain dead from VEM people as being typical of the consequences of the defeat persistent, though not established to the virus. Detection of different time of occurrence of such foci of inflammation in the same case is evidence of at least two exacerbations persistent process. On this same point, and clinical observations cases with repeated, often mild emerging tensions in stages ensuing intermission after acute VEM or chronic stable flow. And in some cases, prolonged exacerbation took slowly progressive type of fatal within the next six years or more. This indicated remittent course during the sub-acute VEM, pathogenetic mechanisms which probably was the peculiarities of persistent «virus VEM», with passages from the dormant latent chronic to slow infection. Noted the great similarity of morphological patterns VEM and tick-borne encephalitis (TBE), progressive clinical forms (PFTBE) belong to a slow infection. Distinctive was the lack of micro thrombosis vasculature of the brain in VEM, although both encephalitis were characterized by multiple small, so-called encephaloclastic foci of brain lesions [13].

According to immunogenetic conceptions of the VEM nature [6], the primary factor encephalopathy with organic neurological micro symptoms (ONMS) is considered a genetic dysfunction of the immune system (the limitation of the production of the gene IFNγ and increase intrathecal synthesis IL18), an extreme expression of which are acute inflammation in stressful situations (up to 30% of patients), or the development of degenerative forms of diseases. When the inflammation characteristic are the breakdown intrathecal immune tolerance and development of local immune response due to the proliferation immune reactive brain cells on infectious allergic

type. According to the author of the hypothesis V.L. Osakovsky (2011) factor that triggers the VEM disease process, is a viral infection of the nature of which does not matter, because VEM is an autoimmune disease [6,7].

Analysis of the course and outcomes of encephalopathy clinical forms VEM in condition, close to chronic stable VEM, gives rise to the hypothesis primary chronicity of latent, clinically unborn or even asymptomatic, which faces the problems of mixed pathologies, differential diagnosis and pathogenesis of fatal of progression of VEM (1,2,3).

Retrospective analysis of long-term observations in the foci of VEM in the process of clinical and epidemiological monitoring of the disease showed that the similarity authentic, possible and probable cases can be found in the trends for change of stable type of clinical course VEM in progressive [2,3]. In this process occur progressive forms of sub-acute and chronic VEM (PFVEM) like PFTBE, with the same characteristics slow infection. However, in the period of formation of chronic VEM after acute, current sub-acute or primary chronic clinical picture of VEM often takes the stable, «frozen» status typical VEM complex syndrome, therefore it is more convenient for clinical monitoring and comparative analysis of VEM morbidity allocate two basic types of chronic VEM:

Gradually, the long-term upward (relatively benign) progredient course (GLU type), which is characteristic also for torpid encephalopathies and smoldering encephalitis.

slowly and fatally (malignant) progressive (MFP type), continuing for not more than 6 years, in fact, characterizing the blurred chronic course on a background of chronic stable that has similarities with over slow infections;

Our task was to establish how often these two types of currents in the epidemic process of VEM for a certain period of time.

Material and methods

Clinical and epidemiological study we involved a retrospective analysis of the archive of the medical histories of the patients with a diagnosis of VEM, charts of ambulatory monitoring in expeditions VEM patients and high-risk patients, manifested with VEM from the 1940s to the present time. For analysis of the incidence, morbidity, mortality VEM in dynamics, we chose 456 patients from 1453 patients VEM database, most fully meet the criteria for probable, possible and authentic VEM. The reliability of a diagnosis of VEM confirmed by documented clinical, pathological, laboratory and epidemiological materials.

Have studied the outcomes of the disease - the duration of acute, sub-acute and chronic stages, stage of intermission and, where possible, of the earlier stage of torpid encephalopathy long before to the onset of the encephalomyelitis. An attempt is made to start tracking stage slowly and fatally progredient (MFP) type of course, to estimate its duration and the illness in General. Identification of the dynamics of the observation of a patient with a diagnosis of VEM accession of a neurological syndrome in long-term stable course chronic VEM contributed to the forecasting of change of type of the course on slowly progressing.

Statistical processing of materials of research conducted using the program «Statistics», the

selection of the group is confirmed when the P-value was less than the threshold level of error of 0.05.

Results and discussion

We have 456 selected patients on the following groups: group 1A - 56 now living with the diagnosis close to an authentic VEM (20 - DFT, 14 - PCF, 19 - PSF, 3 - TVEM with the transition in SPF), with onset of illness from 1950 to 2005, and group 2A - 10 dead from VEM from 1994 to 2012, with the onset of the disease from 1991 to 2010 (i.e. a total of 66 patients with authentic VEM), distributing these groups of patients course on long-term stable (group 1A) and a slowly progressive fatal (group 2A).

Acute and sub-acute VEM with rapidly progressive, fatal from 4 - 8 months up to 27 months duration of the disease was observed in 4 women group 2A (17,46,48 and 49 years) in 1991, 2003, 2008, 2010, and 37-year-old man in 1992. The seven patients out of 10 patients of the second A group with slowly progressive course developed dementia. The disease lasted from 4 months for 8 years, and only in one case - 32 years (terminal stage MFP from him - 8 months).

All 20 patients from the first-A group with the DPF and 19 patients PSF marked the long-term stabilization stage, only two of them with DPF are in a nursing home v. Sosnovka, and in one patient in 2012 notes state, threatening the transition to the terminal stage of VEM. Patients with PSF predominantly located in constant treatment in a psychiatric hospital in Vilyuisk, rise of neurological symptoms was observed.

For a retrospective analysis of the two main types of current archive VEM database we considered two other groups of patients died from VEM: in group 1B (table 1) included 54 patients, characterized by a marked clinical VEM complex syndrome authentic VEM: Parkinson syndrome on the background of different severity pyramid or (rarely) cerebellar-pyramid disorders, cognitive disorders, moderate to extent expressed dementia, pseudo-bulbar, at least - bulbar syndrome, sometimes amyotrophic syndrome to the degree of manifestation of the syndrome ALS. Group 2B amounted to 252 patients died from VEM with moderately expressed authentic VEM complex syndrome (table 2).

Table 1

The average age at onset, and the life expectancy of 54 patients died from Viliuiski encephalomyelitis (VEM) with the expressed complex syndrome of authentic VEM and mainly slowly and fatally progressive form of type duration
(from the VEM database from the1940s until 2012)

Distribution by gender	Age of onset of disease (years)	life Expectancy at the onset of the disease
Men	31±7,9	19,79±3,52
Women	34,4±9,51	14,92±9.48

Table 2……

A third group comprised 94 living patients registered with possible VEM: 58 patients with SPF and 36 patients with TVEM. Mainly they have the disease onset until 1990, for stable VEM, with the severity of VEM complex syndrome much smaller, in comparison with the patients in groups 1A,2A, 1B, 2B. As can be seen from table 1, a slightly lower life expectancy was observed in women (14,92±9.48) with the expressed VEM complex syndrome. And for men, despite earlier VEM initiation, but later accession to low spastic parapareses other syndromes, as extrapyramidal, dysarthria, pseudobulbar, cerebellar, amyotrophias, bulbar, cognitive disorders average length of life was more (19,79±3,52). The average life expectancy of men and women in patients with moderately expressed VEM complex syndrome (table 2), little different from that of women with pronounced VEM syndrome, we explained by the development of slowly progressive VEM most of these patients on the background of previous stable VEM course.

Of 456 VEM patients long-term stable VEM current was found in 237 patients and slowly progressing at 219, which lasted from a few months to 6 years.

It is noted that in a number of patients of 219 (165) slowly progressing VEM developed after several years of stable chronic VEM course (from 1 to 16 years to less than 21 years). Often such a malignant change of course occurred at the background of cold, hard current influenza or pneumonia, rarely trigger factors served pregnancy and heavy labor in women, cranial trauma. Manifested slowly progressive course lasted an average of six years.

Figure 1 shows data of a retrospective analysis of the VEM database of clinical and epidemiological monitoring VEM - comparative graph of morbidity by year as 150 living patients (with VEM onset from 1953 till 2012)and 306 (54 больных1Б group and 252 patients group 2B) died from VEM (after various duration periods of the disease).

Figure 1….

Living VEM patients, as indicated above, are distributed on the possible (94 patients of group 3) and authentic VEM (56 patients of group 1A). Died from VEM patients were included for

corresponding to the criteria's of an authentic VEM. This chart shows how from 1950 to 1990 the incidence of different clinical forms of VEM prevailed tend to develop slowly and fatally progressive type of course, with peaks of this type MFP in the mid-1950s and the 1970s Marked decline in the VEM incidence with the GLU and the MFP types of course similar to its rise from the 1940s.

Below are the data on cases of slow progredient VEM, 1991-2010 (table 3). All these cases are differed by a shorter duration of illness prior to death (2 months, up to 8 years), but one is 32 years. However, in the latter case, as mentioned above, stage of fatal slow VEM manifested later 17-18 years of steady course of SPF and 13 years preceding the stage torpid encephalopathy with ONMS-3-4 degrees of severity, and continued in a more clinically severe form about 8 months. Development MFP final stage was noted at the background of previous stable chronic VEM and in cases with a total duration of VEM six and eight years.

Table 3……

In the cases № 8 and № 9 includes data of the patients with acute and subacute VEM women, 17 and 47 years, and died for over 4 months and 8 months further development of VEM. But in both cases was observed fatal disease exacerbation after a phase of stabilization occurred on a background of intensive treatment in the neurological clinic of the Republican Hospital №2, Yakutsk. In one case, the enhancement of the MFP was the aspiration pneumonia due to traumatic iatrogenia, in the second traumatic long trip from Yakutsk to Vilyuisk in the not comfortable car. Both cases have been confirmed by the data of pathomorphology, where registered inflammatory necrotic encephaloclasytic foci mainly in the brain stem and hypothalamus including that was probably a reflection of the development of the pathological condition incompatible with the survival, despite resuscitation. These are conditions that are characteristic of slow infections, causing the proximity of death.

Also in the cases № 1, № 6 and № 10 acute and sub-acute onset of the disease with mild inflammatory changes in liquor (protein from 33 up to 99 mg/l, lymphocytic from 1 to 49 cells in 3 mm3, positive oligobands IgG to VG), marked atrophy of the cerebral cortex to MRI, psychotic episodes and increasing the degree of intensity of the VEM complex syndrome were progressed to severe disorders, and in subsequent 8-20 months were characterized by symptoms of the typical VEM MFP forms.

In half of the other cases VEM MFP (№ 2, № 3, № 4, № 5, № 7) the beginning of VEM was gradual, and torpid encephalopathy status previously to severe disorder was registered in the cases № 2, № 3 & № 7 within 8 months, 13 and 26 months, respectively.

It is very likely that torpid encephalopathy stage with ONMS preceded the development of VEM with acute and gradual beginning in other cases too, because almost all (except one - № 8) of the patients were descended from sustainable foci of VEM, some of them had long inner families contact with affected by authentic VEM relatives or co-workers (such as in cases№ 1, № 2, № 3, №

4, № 5, № 6, № 9). They were, however, just historical data, and these patients were not examined by a neurologist before detection of VEM.

In these cases of the progressive forms of VEM MFP type (table 3) 8 people have manifested VEM in place of residence in the old strongholds VEM foci of Vilyuisky, Verkhne-Vilyui and Njurbinsky uluses, and in two cases they were taken ill in other villages of the same or a neighboring district. But in the last three cases all patients were sick in Yakutsk, one of them, a 17 year old girl, was from the Njurbinsky district village free of VEM. Manifestations of an authentic VEM cases in Yakutsk were very rare, and such increased against this background looks quite vividly. The probable explanation of this fact - increased migration of population from rural to urban areas in recent years, and the change of factors of risk of the disease in healthy carriers of the alleged VEM pathogen.

Observations on the possibility of transition benign, a steady course of VEM (GLU type) in fatal progredient course (MFP type), are the most powerful factor that compels us to continue medical examinations of people at risk of VEM, the number of which can fluctuate greatly depending on the possibilities of the group of clinicians and researchers.

Conclusion

Infectious-allergic concept of the VEM nature [6] recognizes a variety of infectious agents in the possibility to start of the pathological process in VEM, appealing to the development of VEM from torpid, genetically caused immunodeficiency encephalopathic states. However, this encephalopathy may be a manifestation of latent, with a transition to primary chronic infection, as it is established, for example, with herpes.

Detection of intrathecal synthesis anti herpetic IgG antibodies in the cerebrospinal fluid of VEM patients over the GLU and the MFP types by isoelectric focusing oligobands method (6,7) probably indicates the current, unfinished process of inflammation in the brain, at the same time no one found antigen HV nor by polymerase chain reaction (PCR), nor in immunocytochemical morphological studies of the brain tissue of VEM patients.

Data our analysis in this work may indicate the variability of the properties of the pathogen VEM in its epidemic process, giving certain features for the epidemic VEM process. The appearance of these «features» could affect the spread of the pathogen with the new hosts in the other geographical and ecological niches, and the likelihood of comorbidities and immuno-genetic rearrangements virus carriers and likely other unexplored factors.

In the 1950s - 1960s, increased migration has led to the meeting of the virus unprotected from it new people and, as a consequence, the epidemic spread migrants-vector management (essentially by healthy carriers of infection) to other areas of the Vilusk and then the Central group regions of Yakutia. In the period from 1954 to 2012, was distributed, parallel to each other VEM cases with malignant, slowly and fatally progressive (MFP) and benign, gradually progressing (GLU) types of flow VEM in exposed populations in new regions. The emergence of the MFP by type of slow infection continues to occur in a few cases since the beginning of the 1990s and, although rarely, up to the present time. The most illustrative VEM MFP type cases were registered in 2003, 2008, 2010.

Wide clinical continuum and clinical polymorphism of VEM finds confirmation in identifying torpid encephalopathic VEM forms, progressing in their dynamic clinical observation [3]. Risk factors for the progression of stable VEM course are: 1) repeated VEM exacerbation; 2) the progression of the symptoms of involving in pathological process of the lower spinal motoneuron; 3) the development and progression of dementia mixed type; 4) the depletion of neuroimmunoendocrine protective mechanisms; 5) joining of intercurrent diseases, that reduce the resistance of the organism.

Currently necessary to continue the clinical and epidemiological VEM and risk groups monitoring with the introduction of latest technologies in examination of each VEM case and comprehensive scientific study, for the validity test. Only such a relentless approach to the VEM will allow to approach to the solution of the etiology and pathogenesis of this insidious disease of Central nervous system of the person of Yakutia region, to develop modern prevention and treatment, with more precision diagnose and predict inter vivos the VEM MFP type of course and make reliable predictions prospects the development of the epidemic process of the disease. Preventive measures in VEM should be directed to the VEM risk group, further comprehensive study of which it is necessary to pay attention to.

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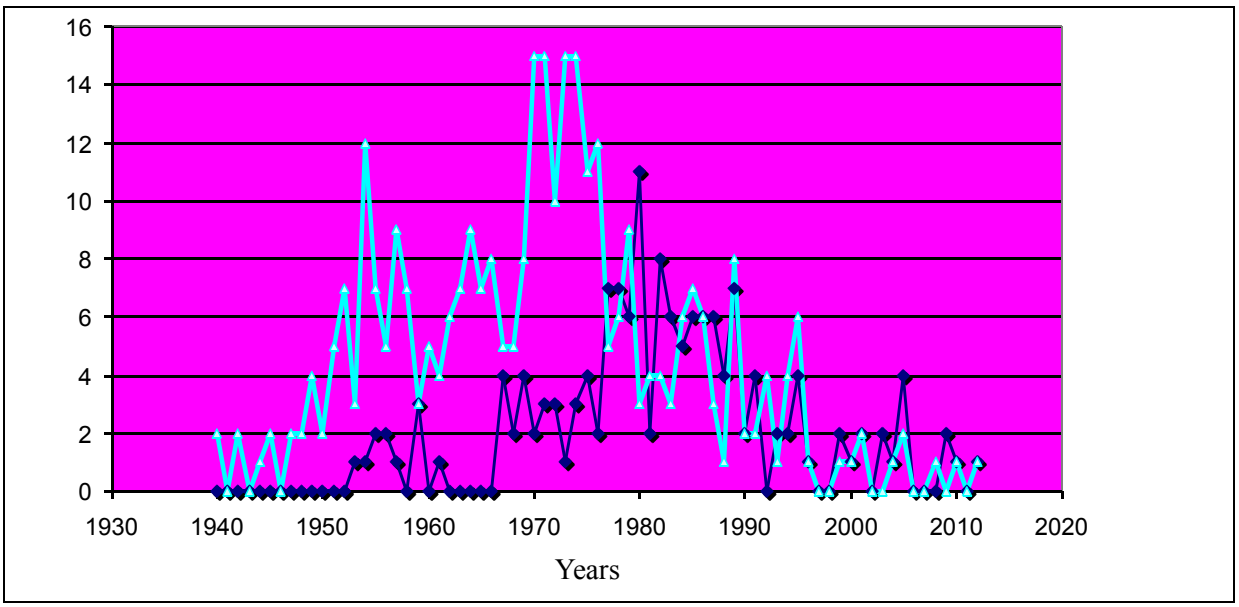
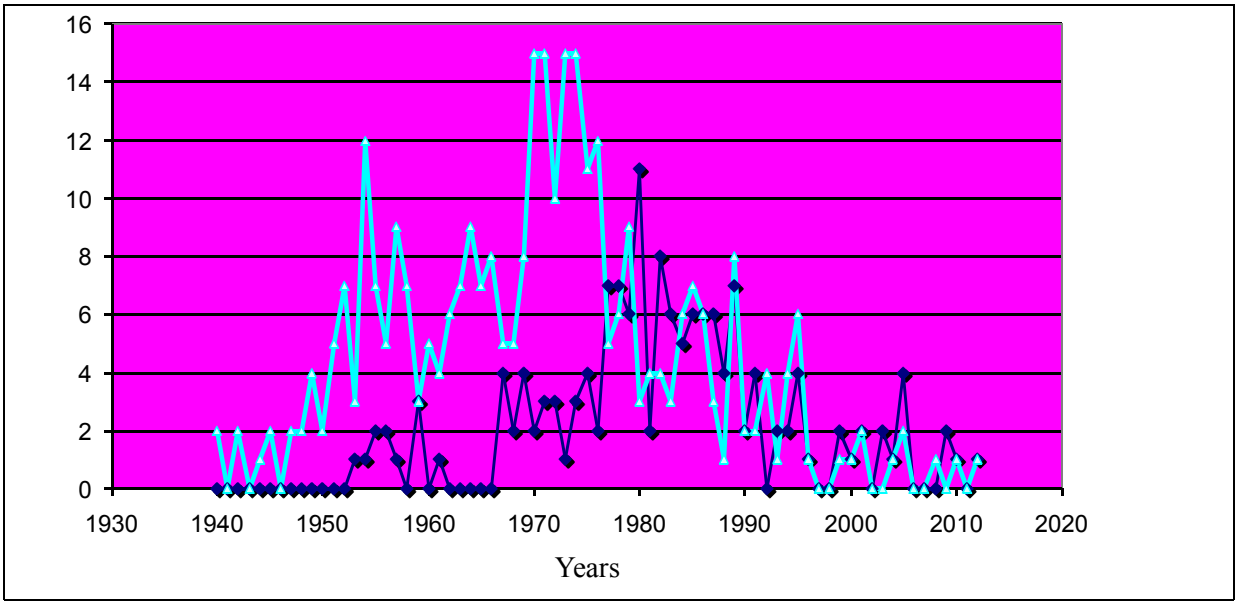


Fig.1. Schedule of morbidity by year of the150 living patients of the possible and authentic VEM (dark blue line) and 306 of the dead cases with a diagnosis of authentic VEM affected in the period from 1940 till 2012. The abscissa years, on the axis of ordinates abs number of VEM patients in a year.



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