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Chronic Herpesviral Neuroinfection and Symptomatic Epilepsy (Literature Review) and The Results of our Own Research

[1]Adambaev Z.I., [2]Kilichev I.A., [3]Ismailova M.O., [4]Khudoibergenov N.Yu., [5]Niyazmetov M.R.
[1]MD, Associate Professor, the Neurological Clinic of General Med Standart, Tashkent, Uzbekistan
[2]MD, Professor of the Department of Neurology and Psychiatry of the Urgench branch of the Tashkent Medical Academy, Urgench, Uzbekistan.
[3]Assistant of the Department of Histology, Urgench branch of the Tashkent Medical Academy, Urgench, Uzbekistan.
[4]PhD, Associate Professor, Head of the Department of Neurology and Psychiatry of the Urgench branch of the Tashkent Medical Academy, Urgench, Uzbekistan.
[5]PhD, Associate Professor of the Department of Neurology and Psychiatry, Urgench branch of the Tashkent Medical Academy, Urgench, Uzbekistan.
E-mail: zufargms@mail.ru

Abstract: The article provides literature data on the incidence of symptomatic epilepsy in various types of chronic herpetic neuroinfection. It also provides data from our own studies of patients with symptomatic epilepsy comorbid with chronic herpesvirus infection. It was revealed that in patients with symptomatic epilepsy prone to pharmacoresistance, the titers of immunoglobulins G of the Herpes and cytomegalovirus viruses exceed the norm by more than 5 times.

Keywords: Chronic herpesvirus neuroinfection, herpes, cytomegalovirus, symptomatic epilepsy, pharmacoresistance.

Introduction

Herpesvirus infections (HVI) are an important medical and social problem. According to WHO, up to 90% of the world's population are infected with viruses of the herpes family, and mortality due to herpes viruses ranks second after influenza [1]. Herpetic encephalitis (HE) is the most common CNS infection in Europe and North America. The specific gravity of GE in the structure of viral encephalitis is about 20%. In Russia, about 20 million people suffer from various forms of BBVI [2, 3]. Human herpesvirus infections (HVI) are a group of anthroponous infections characterized by a chronic recurrent course and lifelong persistence of pathogens in the body [4, 5, 6]. At the present stage, 8 antigenic BBVI serotypes are known: herpes simplex viruses type 1 and 2 (HSV type 1 and HSV type 2), chickenpox - herpes zoster, cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes viruses of the 6th, 7th and 8th types (HHV type 6, HHV type 7 and HHV type 8) [7].

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CNS damage with symptomatic epilepsy of various types of herpesviruses

Herpes simplex viruses type 1 and 2

In the presence of HSV-1 infection, the prognosis for life and health is more favorable than with HSV-2. HSV-1 infection usually manifests itself as a localized form of neonatal herpes, and HSV-2 often causes the development of disseminated form of infection and herpetic encephalitis. Herpetic damage to the central nervous system poses the greatest threat to the health of patients with a mortality rate of up to 20% and a frequency of disability - up to 50% of patients. Clinically, herpetic encephalitis (HE) is characterized by four main syndromes: syndrome of impaired consciousness; hyperthermic syndrome; convulsive syndrome; focal disorder syndrome.

With HE, focal neurological symptoms develop in the form of hemiparesis, and tetraparesis can also be observed. The oculomotor and bulbar nerves may be affected, suggesting brainstem involvement. Paresis of the type of hemiplegia, asymmetry and loss of reflexes, the appearance of pathological reflexes (more often from the extensor group) are possible. A feature of GE is persistent convulsive syndrome, which is difficult to stop with modern anticonvulsant drugs.

Convulsions are more often generalized. Hyperthermic syndrome is also a characteristic feature of HE; however, sometimes there are so-called “cold” HEs [8].

Chickenpox - is an anthroponous highly contagious viral infection accompanied by a febrile reaction, moderate symptoms of general intoxication and a characteristic maculopapular and vesicular rash [9]. Chickenpox is a disease caused by the Varicella Zoster virus (VZV). It is a large filterable virus (210 to 250 μm) that belongs to the alpha herpesvirus family and causes two different diseases: chickenpox and herpes zoster [9]. The defeat of the central nervous system in chickenpox is usually difficult. The most common neurological complication in children with chickenpox is encephalitis, which accounts for 75% among other neurological syndromes, arising from the 4th to 6th days from the development of the rash and in 76% of cases occurs in children under the age of 7 years. The disease in 83.6% of cases is characterized by the development of a cerebellar (cerebellar) form with ataxic disorders and reflex pyramidal disorders, an outcome in recovery in 100% of cases and much less often (in 16.4% of patients) - a cerebral form of encephalitis with the development of impaired level of consciousness and seizures, with an outcome in epilepsy in 60% of cases [10, 11, 12].

Cytomegalovirus encephalitis

Latent CMV is often present in the majority of the population, especially in the elderly. A study in the United States showed that 60% of clinically healthy people were CMV seropositive. If CMV was found in children in 36% of cases, then after 80 years - in 90%. Usually, CMV clinically manifests itself as an opportunistic infection with a significant decrease in immunity and most often accompanies AIDS. There is also evidence that CMV

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can be reactivated by stress and aging [13]. CMV has tropism for both neurons and glial cells [13]. Damage to the nervous system CMV most often manifests itself in the form of one of three syndromes: encephalitis with or without meningitis and / or ventriculitis; polyradiculopathy with damage to the lumbosacral roots and multiple mononeuropathy [14]. Cases of CMV of acute widespread myelitis have also been described [15]. To establish the diagnosis of cytomegalovirus damage to the nervous system, it is necessary to determine the presence of this virus in the CSF by PCR.

Morphologically, encephalitis in CMV infection is manifested by areas of necrosis, loss of neurons and periventricular demyelination; the pathological process also involves the gray matter and ventricular ependyma [16].

We did not find any information that during mono CMV infection of the central nervous system any convulsive manifestations develop in the literature. There is information on the detection of symptomatic epilepsy in CMV mixed herpesvirus infection [17].

Epstein-Barr virus- it is the human herpes virus type 4, which is considered the main culprit in the development of infectious mononucleosis and tumors, in particular Burkitt's lymphoma, as well as multiple sclerosis (MS) and chronic fatigue syndrome. This is the most widespread virus on the planet, the carrier reaches 95% of the world's population.

In population studies, the incidence of epilepsy in MS ranges from less than 1 to 7.8% [18]. According to a meta-analysis of population studies, the incidence of seizure disorders in MS was 3.09% [19].

Partial epilepsy is expected in MS [20]. Indeed, most studies noted that the most common type is secondary generalized seizures, often simple or complex partial seizures are observed [20, 21]. According to the Mayo Clinic, generalized seizures were noted in 68.6%, simple or complex partial seizures - in 21.6% [22]. However, given the anatomical variability in the localization of plaques, MS seizures are highly variable. Epilepsia partialis continua, myoclonic, absence, various reflex and other seizures have been described in MS (up to 10% of seizures remain unclassified) [23, 24, 25]

HHV type 6. Studies conducted in Japan have shown that the prevalence of such forms of HHV type 6 infection is 0.2% of cases among infected patients, in the UK this figure reached 0.8% and 1.5%, respectively. Children hospitalized with convulsive syndrome or encephalitis were more likely to have type 6 HHV infection integrated into the human genome, the rate of which reached 3.3% [26].

In type 6 HHV infection, CNS pathology is accompanied by memory impairment, fatigue and difficulties in cognitive activity, seizures, and acute limbic encephalitis [27].

Convulsions are a typical clinical manifestation of this infection, and MRI of the brain in such cases demonstrates the involvement of the median regions of the temporal lobes of the brain. Evidence has emerged that HHV 6A plays a role in the development of multiple sclerosis (MS), often acting as an activator of other viruses such as EBV or endogenous

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retroviruses (HERV-W). Currently, much attention in the development of MS is given to the role of HHV type 6, along with EBV, Chlamydophilla pneumoniae, and human endogenous retroviruses (HERVs) [28, 29].

HHV type 7 and 8.

To date, HHV-7 is classified as a member of the β-herpesvirus subfamily. Seroepidemiological studies have shown that HHV-7 is widespread. The isolation rate of HHV-7 in children aged 0-11 months is 0%, 12-23 months - 50%, 24-35 months - 75%, over 36 months - 100% (in contrast to HHV-6, in which seroconversion observed before the age of 12 months). In the blood of donors, HHV-7 DNA was detected in 97.3% of the examined individuals, while the carriage of the HHV-7 genome was observed for 53 weeks.

Thus, HHV-7 persists in the host after the primary infection and is most often isolated from healthy adults. The role of HHV-7 in pathology has not been studied. HHV-7 is associated with lymphoproliferative diseases, chronic fatigue and immunodeficiency syndromes [26].

HHV-8 is a herpesvirus associated with Kaposi's sarcoma. The virus is widespread in the population: more than 25% of the adult population and 90% of HIV-infected have antibodies to the lytic proteins HHV-8 [26].

There are no data in the available literature on the influence of HHV type 7 and 8 on the development of symptomatic epilepsy.

Pathogenetic mechanisms of epileptogenesis of herpesvirus neuroinfection

After the primary infection of a child with HHV type 6, several options for the development of the disease are possible: from the classic Roseola infantum (sudden exanthema) to the onset of undifferentiated diseases accompanied by a febrile state without a visible focus of infection, convulsive syndrome and rash.

According to a number of authors, from 13% to 33% of the first episodes of febrile seizures occur during the manifestation of primary infection with HHV type 6. The trigger of almost one third of all seizures recorded in children under 2 years of age is HHV type 6, which indicates the active reproduction of the virus in the central nervous system (CNS) [30].

It has been shown that certain structures encoded by the HHV type 6 genome are identical to the antigens of myelin basic protein. Importantly, both the number of T cells and the titer of antibodies to these amino acid sequences were significantly higher in patients with MS. In addition, glial cells infected in vitro demonstrated the ability to weaken the cellular immune response and increase the number of oligodendrocyte markers, which indicates the possibility of HHV type 6 infection to influence the mechanisms of nerve tissue repair [26, 31].

There are numerous data on meningitis, encephalitis, encephalomyelitis associated with herpes infection of the 6th type [32, 33].

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A group of scientists from the National Institute of Neurological Disorders in Bethesda, USA (Viral Immunology Section, National Institute of Neurological Disorders and Stroke, NINDS, Bethesda) attempted to find out how the herpes simplex virus type 6 can enter the brain tissue. The authors, after analyzing samples from the nasal mucosa, found HHV type 6 in it in 50% of cases.

In further experiments, the authors found that glial cells accompanying the olfactory tract from the nasal receptors to the brain are sensitive to this virus and can serve as conductors for it to penetrate into neuroglial cells: oligodendrocytes, microglia, and astrocytes - phagocytic macrophage cells of the central nervous system [34].

In general, viruses of the Herpes viridae family have high neurotropic properties; they aggressively invade the central nervous system through the blood-brain barrier, infect and subsequently multiply in the neurons of the brain. In human CNS cells, certain viruses (HSV-1, HSV-2, EBV, VVZ, CMV, HHV-6, HHV-7) can remain latent for a long time after the initial infection.

This ability of herpes viruses suggests the emergence of latent and indolent neuroinfections, the primary chronicity of herpesvirus encephalitis with frequent relapses of the disease in the absence of adequate antiviral and immunomodulatory therapy [35, 36] and is one of the causes of neurodegenerative processes in the central nervous system [37, 38].

The immune system tries to fight herpes viruses and mistakenly attacks the brain - specific antibodies are produced against the proteins of the limbic region, especially targeting the hippocampus and amygdala, which leads to the triggering of an autoimmune reaction. Inflammatory cytokines, including interleukin 1β, contribute to damage (neuronal dysfunction) and gradual death of neurons in the limbic system. Epileptogenesis in chronic HE is associated with damage to hippocampal neurons. Intrathecal activation of cellular and humoral immunity is the reason for the persistent course of chronic HE and the development of resistance to antiviral drugs [39].

When the herpes simplex virus type 6 enters the nerve cell, the level of intracellular calcium increases. leading to water-electrolyte disturbances in the synaptic tissue, which results in convulsive syndrome when infected with HHV type 6 [40].

Diagnostic moments of herpetic neuroinfection with symptomatic epilepsy

Brain biopsy, serological study of intrathecal antibodies to viruses of the Herpes viridae family, and detection of virus DNA in the cerebrospinal fluid [41, 42] undoubtedly play a leading role in the diagnosis of chronic HE, however, due to invasiveness, their implementation is available only under stationary conditions. At the same time, PCR detection of viral DNA in the cerebrospinal fluid in chronic HE associated with mixed herpesvirus infection can give false negative results [41, 43, 44]. These false responses of molecular diagnostics of the DNA of herpes viruses in the cerebrospinal fluid can lead to

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errors in the clinical diagnosis and incorrect treatment tactics, as well as to the premature termination of specific antiviral and immunomodulatory therapy [43, 45].

To confirm the clinical neurological diagnosis of chronic EH with symptomatic epilepsy on an outpatient basis, neuroradiological studies play an important role: high-field magnetic resonance imaging (MRI) of the brain with gadolinium contrast, magnetic resonance spectroscopy [46, 47], electroencephalography (EEG), video EEG monitoring, study of the titer of antibodies of the early and late immune response to herpes viruses in blood serum (including antibody avidity), immunological study of the state of T-cell, humoral, phagocytic immunity, cytokine status [48, 49, 50].

The diagnosis of acute herpes infection caused by HHV type 6 is based on a combination of clinical data and a set of laboratory methods. One of the most common immunobiological methods for detecting specific antibodies is the enzyme-linked immunosorbent assay (ELISA). Its sensitivity is 99%, specificity is 95%. Serodiagnostics provides retrospective information about the presence of the virus. The disadvantages of serological tests in the diagnosis of opportunistic infections are: a high frequency of carriage in healthy people, the presence of IgG antibodies means only a response to the infection, but does not indicate the activity of the infectious process, the absence of antibodies does not mean the absence of the pathogen (immunodeficiency causes a decrease in antibody production), chronic infection does not always accompanied by the detection of IgM antibodies, do not allow to distinguish between HHV 6A and HHV 6B.

If it is recommended to use the method of polymerase chain reaction (PCR), ELISA and the reaction of immunofluorescence (RIF) as a screening method, then the method of detecting herpesvirus antigens in blood cells on sensitive cell cultures is used as a confirmation method [51, 52].

Treatment of herpes neuroinfection

Long-term latency of herpes viruses in the mediobasal (limbic) regions of the brain may be the source of the development of symptomatic temporo-lobe mediobasal epilepsy, resistant to antiepileptic therapy [53].

Therefore, the treatment of especially chronic and recurrent forms of herpes infections should be complex with the use of antiviral drugs with different chemical structures, inducers and donors of interferons, and given the presence of changes in immunity, it is advisable to prescribe immunomodulators. The use of existing vaccines and the emergence of new ones will help remove the urgency of the problem of recurrence of the disease [52].

Thus, from the above literature review, it can be concluded that herpesvirus infections are widespread among the population - up to 90%. Herpetic damage to the central nervous system poses the greatest threat to the health of patients with a mortality rate of up to 20% and a frequency of disability - up to 50% of patients.

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Among the lesions of the central nervous system, herpetic encephalitis is detected, corresponding to the classic example of encephalitis. It is characterized by four main syndromes: syndrome of impaired consciousness;
hyperthermic syndrome; convulsive syndrome; focal disorder syndrome. The following herpes forks lead to herpesvirus encephalitis: HSV type 2, CMV, EBV, HHV type 6; and herpesvirus symptomatic epilepsy leads to: HSV type 2, EBV and HHV type 6. However, HSV type 1 and CMV are often detected in symptomatic epilepsy as a mixed herpesvirus infection.

Viruses of the Herpes viridae family have high neurotropic properties, they aggressively invade the central nervous system through the blood-brain barrier and along the olfactory tracts from nasal receptors, infect and subsequently multiply in the neurons of the brain. They can remain latent for a long time after the initial infection. This ability of herpes viruses suggests the emergence of latent and sluggish neuroinfections, the primary chronicity of herpes-viral encephalitis with frequent relapses of the disease in the absence of adequate antiviral and immunomodulatory therapy and is one of the causes of neurodegenerative processes in the central nervous system.

At provoking moments (hypothermia, nervous overstrain, intercurrent infection, etc.), the immune system triggers autoimmune reactions specifically targeted to the hippocampus, amygdala and brain myelin with the formation of areas of necrosis from 3 to 5 ml according to MRI data.

Epileptogenesis in chronic herpesvirus enceflitis is associated with damage to hippocampal neurons. In nerve cells, the level of intracellular calcium increases, leading to water-electrolyte disturbances in synapses with the development of convulsive syndrome during infection, which is the cause of the development of resistance to anticonvulsants.

Output. If patients have symptomatic epilepsy, and especially with its pharmacoresistance, it is necessary to check the patient for the following types of herpes: HSV type 2, CMV, EBV, HHV type 6. In the presence of these types of herpes, it is necessary to carry out adequate antiviral and immunomodulatory therapy.

Below we present the results of our own research.

Recently, it has been shown that viral infection plays a significant role in the chronicity of epilepsy and the development of drug resistance [54, 55, 56, 57]. However, the role of viral infection in the pathogenesis of symptomatic epilepsy has not been sufficiently studied, which indicates the relevance and timeliness of the work being done.

The Aral Sea territories are considered to be ecologically the most problematic regions, both from the point of view of natural and anthropogenic conditions. The extreme natural conditions characteristic of these arid zones negatively affect the human body, increasing the likelihood of illness in the local population. Against this background, significant anthropogenic changes significantly worsen the quality of the environment, which

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is an additional reason for the decline in the level of health of the population, as well as the basis for classifying these territories as regions of ecological crisis and ecological disaster [58].

The aim of the study was to study the clinical and electroencephalographic manifestations in patients with symptomatic epilepsy of viral etiology in the Aral Sea region.

Materials and Methods

90 patients with symptomatic epilepsy of viral etiology were examined. The age of the patients ranged from 14 to 60 years, the average age was 26.1 ± 1.9 years. Among the surveyed there were 50 (66.7%) men and 40 (33.3%) women.

The patients underwent neurological, clinical and laboratory, electroencephalographic examinations. The results obtained were compared with those of the control group (30 people), which consisted of practically healthy people of the same sex and age. For statistical processing of the results, we used correlation analysis and Student's t test.

Results

Neurological examination of patients revealed various neurological changes, namely: disseminated cerebral microsymptomatology (in 50%), discordant (in 33.3%), mild pyramidal insufficiency (in 16.7%), intracranial hypertension syndrome (in 11.1 %). The distribution of patients by the nature of seizures showed that the leading clinical seizures were generalized seizures in 61.1% of patients and patients with simple and complex partial seizures (38.9%). The frequency of partial seizures with secondary generalization was 44.4%. 27.8% of patients had polymorphic seizures (simple partial in combination with absences or, in combination with primary generalized tonic-clonic seizures).

Patients with disease duration up to 5 years accounted for 63.3%. In 27.8% of patients, the first seizure occurred in the acute period of neuroinfection, and in the remaining 72.2% in the long-term period: from six months to 10 years. The frequency of seizures at the time of examination in patients varied and the majority (66.7%) of patients had rare seizures (once a month or less), the same group included patients with newly diagnosed seizures. In 20% of patients, seizures were of moderate frequency (from 2-3 times a month), and frequent seizures (1 time per week or more) were observed in 13.3% of patients. When considering seizures depending on the sleep-wake cycle, it was found that in the majority of 88.9%, seizures occurred in the waking state.

We divided our patients in the course of the disease into two types: favorable (63.3% of patients) and unfavorable (36.7%). With a favorable course against the background of anticonvulsant therapy, there was a decrease, a clear confinement to the time of day and a monomorphism of seizures, and a preserved social adaptation of patients. The unfavorable type of course was characterized by an increase in the frequency and polymorphism of seizures with an increase in the duration of the disease, short duration of remission, a tendency to seriality, a status course, and increasing mental changes.

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When conducting a study of immunoglobulins M and G of Herpes and CMV, it was revealed that the IgM indicators were within the normal range, while IgG was increased 4.5 times with a favorable course, and 8.6 times with an unfavorable course.

EEG studies were conducted in all patients with symptomatic epilepsy. Moreover, if in patients with a favorable course of the disease, mainly acute slow-wave and spike slow-wave complexes were observed, then in patients with an unfavorable course (pharmacoresistant), in addition to everything, multifocality and regionality of foci and hypsorhythmia were observed, which indicated the appearance of many foci of demyelination in the brain and weighting of EEG indicators (table).

Discussion

The Aral Sea crisis has a negative impact on the conditions and quality of life of the population of Central Asia, but most of all affects the health status of people living in the epicenter of the ecological disaster. An increase in the unemployment rate, a drop in income, a decrease in life expectancy, an increase in child mortality, bacterial and viral diseases, etc. - an incomplete list of the consequences of the current ecological crisis [59]. The growth of viral diseases in the Aral Sea region, cause an increase in symptomatic epilepsy of viral etiology, which has its own clinical and electroencephalographic manifestations, which must be taken into account when diagnosing and treating this type of epilepsy.

Table

EEG indices in patients with symptomatic epilepsy

	unfavorable type n = 33	favorable type n=57	control group n=30
Sharp slow-wave complexes	9 (27,3%)	39 (68,4%)	1 (3,3%)
Spike slow-wave complexes	12 (36,4)	14 (24,6%)	-
Multifocal and regional foci	12 (36,4)	4 (7%)	-

Conclusions

1. Seizures in symptomatic epilepsy of viral etiology are characterized by generalized (61.1%) and partial (38.9%) seizures.

2. In 27.8% of patients, the first seizure occurs in the acute period of neuroinfection, and in the remaining 72.2% in the long-term period: from six months to 10 years.

3. Symptomatic epilepsy of viral etiology along the course of the disease is divided into two types: favorable (63.3% of patients) and unfavorable (36.7%) - pharmacoresistant.

4. The IgG level of Herpes and CMV in symptomatic epilepsy of viral etiology with a favorable course exceeds 4.5 times, and with an unfavorable course - 8.6 times.

5. During EEG studies in patients with a favorable course of the disease, mainly acute slow-wave and spike slow-wave complexes were observed, and in patients with an unfavorable course (pharmacoresistant), in addition to everything, multifocal and regional foci and hypsorhythmia were observed.

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