

Review article



PECULIARITIES AT CLINICAL COURSE AND PROGNOSTIC FACTORS OF THE MOST COMMON VIRAL INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

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ABSTRACT

Viral infections of the central nervous system (CNS) are highly varied and in many cases difficult for diagnostics. Recently they have become more frequent in the practice of the specialists in infectious diseases and general medicine. Sometimes they had a motley clinical spectrum in other cases they were so similar that their appearance was a big challenge for clinicians.

The aim of this presentation was to clarify the peculiarities in clinical course and prognostic factors of some of the most widespread viral CNS infections.

In Bulgaria, 400 cases of viral infections of the CNS were registered per annum. The most prevalent of them were caused by Enteroviruses. Encephalitis, caused by Herpes simplex virus type 1 (HSV1) was associated with high mortality and severe residual complications in survivors. VZV provoked benign encephalitis with cerebellitis. Lymphocytic choriomeningitis virus meningitis was characterized with long-lasting meningeal signs and combined with some psychological deviations and focal neurological disorders. Influenza virus rare but serious affected CNS with convulsions, psychotic expressions, stupor and coma.

Prognosis for the severity of viral infections of the CNS was dependent on age, immune status, neurological predisposition and virulence of the etiological agent. Some peculiarities at laboratorial findings, as well as the delaying of specific etiological therapy were important prognostic factors for bad outcome.

Keywords: viral infections of CNS, peculiarities, prognostic factors

Viral neuroinfections are meningitis, encephalitis, myelitis, polyradiculoneuritis and combinations of them. Versus bacterial ones they more often have mild clinical course and more favourable outcome [1]. Prevention with vaccines reduces the rate of viral damages of the central nervous system in Mumps, Measles, Rubella, Chicken-pox, Poliomyelitis, Influenza and Rabies [2].

Viral meningitis has a sudden acute beginning, in

spite of that in some of them, there is prior malaise. Temperature, headache, irritability, vomiting and neurological meningeal signs are present as typical symptoms [3]. Encephalitis is a disease which causes inflammation of the brain tissue; it can be viral, bacterial or immune-mediated in origin [4]. Viral encephalitis usually starts acutely with high temperature. They are manifested with focal neurological deficits as consciousness deteriorations from lethargy to alteration, paresis and paralysis of peripheral and cranial nerves, convulsions [5]. Lumbar puncture is more important diagnostic procedure which is performed urgently upon admission to hospital. Laboratorial analysis, microbiological and virological investigations of the cerebrospinal fluid (CSF) are crucial for the prompt diagnosis [6]. CT of the brain is usually made before the lumbar puncture for excluding space-occupying processes as hematoma, tumour or obstructive hydrocephaly. MRI with or without contrast is a standard method for visualization of intracranial pathology in viral encephalitis [7].

Enteroviral meningitis/meningoencephalitis.

Enteroviruses (EVs) have emerged as one of the important etiological agents for encephalitis, especially in children. They have arant neurotropism. EVs count approximately 100 serotypes and belong to the family Picornaviridae. More often neurotropic are Polio, ECHO (4, 5, 9, 11, 19, 30), Parechoviridae (22, 23), Coxsackie (A9, A10, A5) and EnteroVi (70, 71, 75, 76, 89) [8]. Up to 60% of EV meningitis in age under 3 years are associated with Coxsackie viruses. Men are more affected than women in the warm seasons of the year. EVs meningitis doesn't distinguish from other viral meningitis [9]. The classical triad of meningitis was demonstrated on the background of a sore throat with herpetic enanthem with or without dyspeptic symptoms. The non specific rash could be appeared. Lumbar puncture firstly showed a prevalence of polynuclears which were changed with mononuclears after that [10]. Compared to other viral encephalitis levels of personality change, rashes, and diarrhea are significantly higher in EVs associated encephalitis than in other viruses associated encephalitis [11].

However, studies have shown that neck stiffness is significantly less common in them [12].

Prognosis of unfavorable outcomes – death or neurological sequelae have been associated with younger age (<4 years), the appearance of convulsions, skin rash, myoclonic jerks, and etiological proved EV 71 infection [13]. Peculiarities at CSF are connected with the presence of mononuclear pleocytosis, but in the first 24-48 hours, there is usually a predominance of polynuclears. Sometimes there is a low level of CSF glucosis [14]. The disease has a comparatively mild clinical course, and in regard the outcome, it usually ends with full recovery. Mild intellectual deficit and speech delay is possible in age under 3 years of age [10].

Influenza encephalitis/encephalopathy. Influenza virus belongs to a family of Orthomixoviridae. Three serotypes exist – A, B and C. CNS is affected more often with serotype A, less with B [15]. Involvement of the CNS in influenza virus infection is very rare, but serious with manifestations, such as convulsions, psychosis, stupor, and coma [16]. Encephalopathy/encephalitis appears to be not so common associated with influenza neurologic complication. It is usually defined as altered mental status lasting for more than 24 hours, but its clinical spectrum can vary from mild confusion to behavioral changes, delirium/hallucination, meaningless speech, mutism/aphasia, lethargy, somnolence, and coma [17]. There have been attempts to separate encephalopathy from encephalitis based on the presence of CNS inflammation. For instance, only a few patients with influenza-associated encephalopathy have elevated protein or mild pleocytosis in the CSF. In most cases CSF is normal. Acute necrotizing encephalopathy is a severe type of encephalopathy associated with influenza [18]. Bad prognostic factors are younger age, fast moving mental changes, high level of CNS protein, blood glucosis, aminotransferases and nitrogenous bodies as well as low level of prothrombin time and platelets [19]. The mortality rate of this disease is as high as 30% without treatment [19]. Neuropsychiatric behavior alterations have been associated with influenza as part of the clinical spectrum of encephalopathy/encephalitis [20]. Children or adolescents may present within the first 3 days of influenza with delirium characterized by visual hallucinations, inappropriate laughing or smiling, meaningless words, incoherent speech, and restlessness [21]. MRI scan and EEG are often normal [21].

Herpes simplex virus (HSV)encephalitis. It is one of the most severe infections of the CNS. Despite the presence of the corresponding specific etiological therapy, it is associated with high mortality and heavy residual events. Almost all cases with the exception of these in the neonatal period are due to HSV-1. This is a rare disease – in 1/500 000 per year [22]. Men and women, the both of them are equally affected, predominantly aged under 20 and over 50 years of age. In young age, it usually appears as a primary infection, while in advanced age it is secondary [23]. It habitually starts with high temperature and headache in com-

ination with early neurological manifestations as confusion and personality disorders. This is followed by paresis of cranial nerves, dysphagia to aphagia and ataxia. Meningeal signs are not typical [24]. The disease is rapidly progressed with deploying of focal or generalized convulsions, coma and death. Approximately in one third of cases hemiparesis is established. Less often there is a loss of vision and edema of the papilla of n. opticus [24]. The golden standard for the diagnosis is proving of HSV in CSF by PCR [25]. Neuroimaging as CT of the brain shows temporal and frontal lobes involvement. MRI visualises hemorrhagic-necrotic lesions in the same zones [6]. Mononuclear pleocytosis and mildly elevated protein level are common findings of an analysis of CSF samples, although several CSF samples are acellular or pleocytic with polymorphonuclear predominance at the onset of the disease. Accelerated ESR and leucocytosis in the blood are established, but they are not mandatory [25]. The diagnosis is suspected in any patient with progressive disturbances of consciousness, fever, pathological CSF findings and focal neurological deviations in the absence of any other possible cause. There are no pathognomonic features to be categorically associated with the diagnosis HSV encephalitis (HSE) [26]. Important prognostic factors are: age of patient, degree of disturbance of consciousness at the time of initiation of specific therapy with Acyclovir, focal neurological deficit, convulsions, need of mechanical ventilation, low serum sodium concentration, CSF parameters, GCS scores, early diagnosis and delay between hospital admission and initiation of Acyclovir therapy [26]. Nowadays despite all the achievements in a diagnostic-therapeutic aspect the level of mortality of HSE is high – approximately 19% in treated, and 70% in untreated. A half of survivors have neurological complications [27]. Because Acyclovir is the only opportunity for improvement the outcome of the disease, it should be administered as early as possible even in case of doubt about HSV [28].

Chickenpox encephalitis. VZV is an alfa-herpetic virus. It is extremely widespread in Bulgaria. Neurological complications meet in 1-3 of 10 000 cases. They are demonstrated as cerebellar ataxia and encephalitis. Ataxia appears on the 2-3 day after the starting of the disease but quite often in the beginning. It is accompanied by a headache, vomiting and fatigue [29]. Neck stiffness and nystagmus are observed in 25% [30]. The CSF flows under high pressure with mild lymphocytic pleocytosis – under 100 cells – as well as slightly elevated protein in 20-30%. The level of glucose is normal. The patients recover within 2-3 weeks [31]. In encephalitis new fever wave, headache and deteriorated consciousness appear approximately a week after the chickenpox rash. Convulsions are observed in 29-52% [32].

Except ataxia other neurological manifestations are changes in muscle tone and reflexes, hemiparesis and disturbed consciousness [33]. Neuroimaging investigations show cerebral edema and areas with hypodensity, corresponding to demyelination. The level of mortality is approximately 5%, but more often there is full recovery [34]. The treatment is conducted with Acyclovir [35]. A live at-

tenuated vaccine against Chickenpox exists, but it is not available in our country.

Measles encephalitis. Measles virus causes 4 types of neurological disorders:

- Acute infectious encephalitis
- Acute postinfectious encephalitis
- Subacute measles encephalitis in immunocompromised
- Subacute sclerosing panencephalitis in immunocompetent [36].

Every convulsion during Measles is accepted as a sign of encephalopathy/encephalitis, not as febrile one. Clinical presentations vary from mild confusion to coma and exitus [37].

Laboratorial findings in CSF showed mild lymphocyte pleocytosis and proteinorachie [36].

60% of patients with Measles encephalitis have a full recovery, 25% remain complicated – mental retardation, hearing loss, motor deficit and 15% died [38]. Acute postinfectious encephalitis is demonstrated with meningeal signs, seizures, less often focal motor deficit, neuritis of n. opticus, myelopathy. MRI indicates white brain matter involvement [38]. Subacute measles encephalitis appears 1 to 10 months after acute infection in immunosuppressed people with malignant hematopathy, AIDS. There are myoclonic jerks, tremor, ataxia, apraxia, meningeal signs, decreased cognitive function and refractory local convulsions. Over the course of days and weeks vision and hearing loss, loss of motor activity, and sensitivity are progressing [39]. Subacute sclerosing panencephalitis (SSPE) appears years after the acute Measles. It is progressing to a fatal outcome. Men are more affected than women. Fever, spastic quadriplegia, tonic cramps are demonstrated. From a few months to a year comes coma and death. [40].

Lymphocytic choriomeningitis (LCM). The virus of LCM is representative of the family Arenviridae [41]. Humans can acquire LCM virus during any season, but most LCMV infections occur during the late autumn and early winter months, reflecting the seasonal movement of mice into human homes during the cold season [42]. This neuroinfection is protracted as meningitis or meningoencephalitis and usually ends with full recovery. In general, mortality is less than 1% [43]. It begins with high fever which could be biphasic, very severe headache, myalgia, lethargy, acute catarrh of the upper respiratory tract, repeated vomiting without relief, diarrhea, measles-like rash. Often there are possible hallucinations, distorted coordination, hemiparesis and sensitive deteriorations [44].

First temperature wave's investigations are leucopenia and low level of platelets. Second phase's investigations of CSF show elevated levels of protein and lymphocytes in almost 100%, and diminished glucose in less than 25% [44, 45]. Serological immunoenzyme (ELISA), as well as virologic (RT-PCR) methods, are used [45].

Lymphocytic choriomeningitis (LCM) is rarely fatal; the overall prognosis is excellent. Patients with encephalitis are at higher risk for neurologic sequelae. Convalescence may be prolonged, with continuing dizziness, somnolence, and fatigue [46]. Death may be attributable to complications of encephalitis or to a massive hemorrhagic syndrome [46].

CONCLUSION:

Accurate and timely diagnosis of viral neuroinfections as well as proper therapy is important for the good outcome of the disease. Poor prognostic factors include younger and advanced age, damaged pre-morbid terrain, delayed diagnosis and inadequate therapy.

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