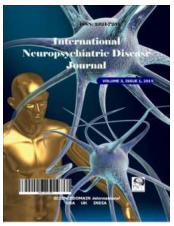

International Neuropsychiatric Disease Journal

9(4): 1-10, 2017; Article no.INDJ.35179
ISSN: 2321-7235, NLM ID: 101632319

The Spectrum of Herpesvirus Infections of the Nervous System in Adult Patients in Ukraine: A Prospective Single Center Study

P. A. Dyachenko[1*] and A. G. Dyachenko[2]

[1]Center of Infectious Disorders of the Nervous System, Kyiv, Ukraine.
[2]School of Medicine, Sumy State University, Sumy, Ukraine.

Authors' contributions

This work was carried out in collaboration between both authors. Author PAD designed the study, collected patients and examined them, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author AGD managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/INDJ/2017/35179
Editor(s):
(1) Weike Mo, Scientific Director for Pharmacogenetics, Molecular Testing Labs, USA.
Reviewers:
(1) Renshan Sun, Third Military Medical University, China.
(2) Shamala Moodley, Mangosuthu University, South Africa.
Complete Peer review History: http://www.sciencedomain.org/review-history/20397

Original Research Article

Received 30th June 2017
Accepted 1st August 2017
Published 7th August 2017

ABSTRACT

Background: Herpesviruses (HVs) are ubiquitous pathogens that infect humans usually during childhood, followed by a life-long persistence in a latent state in many sites of a body including the nerve cells. After reactivation HVs can affect the Central Nervous System (CNS) becoming a major cause of morbidity and mortality worldwide as well as long-term neurological sequelae. Despite being an important public health problem very few population-based studies were conducted so far in the world and none in Ukraine.
Objectives: To explore the clinical features and etiology of herpesvirus encephalitis (HVE) in a prospective single center study from January 2014 to January 2015.
Methods: 107 adult patients with confirmed herpesvirus infection and symptoms of possible encephalitis (CNS lesion) were analyzed in the study. CSF and blood contents, antibody for HVs M and G9 antibody classes, and MRI scans have been studied, but the crucial diagnostic sign was the presence of specific viral DNA in the CSF or blood.
Results: 74 (69.3%) out of 107 patients were females, the male to female ratio was 1:2.2. The

**Corresponding author: E-mail: padyac@gmail.com;*

median age of patients was 36.9 years (range 20-65 years). Most common clinical features were fever, (stiff neck), and focal neurological signs. The genome of HVs was detected in CSF samples obtained from all patients as follows: Herpes simplex virus 1 and 2 – 13 (12.1%), Varicella zoster virus – 2 (1.8), Cytomegalovirus – 14 (13%), Epstein Barr virus – 22 (20.5%), Human herpesvirus 6 – 5 (4.7%), Human herpesvirus 7 – 13 (12.1%). Co-infection (≥ 2 HVs) was observed in 38 patients (35.5%). CSF of 27 patients contained two viral DNA, and 11 – three one in various combination. Human herpesvirus 8 was not found.

Conclusion: The most frequently diagnosed infections in hospital based study were Human herpesvirus 5 (EBV), followed by HSV-1/2, CMV, and HHV-7. Significant part of patients (35.5%) was co-infected with two or three HVs. Predisposing factor for Ukrainian population is sex.

Keywords: Encephalitis; human herpesviruses.

1. INTRODUCTION

Herpesviruses (HVs) are ubiquitous infectious agents belonging to the herpesvirus family (*Herpesviridae*). Primary herpesvirus infection usually occurs during childhood and may cause several benign self-limited clinical manifestations, followed by a life-long persistence in a latent state with possible reactivation in case of immunodeficiency. Serious health problems, including CNS lesions can occur as a result of HVs reactivation. One of the conditions, encephalitis, is a serious polyetiologic inflammatory process of the brain. At present not all the causes of the disease are established. It is well known that they can be infectious and non-infectious. The viral agents of encephalitis vary greatly between countries, with herpesviruses (HVs) being the major etiology in many countries bothdeveloped and industrialized. Herpesvirus encephalitis (HVE) accounts for up to 40% of all viral encephalitis, and are major causes of mortality and long-term neurological sequelae throughout the world even when using antiviral drugs. Since surveillance and recording of herpesvirus infections (HVI) are not common practice, it is difficult to establish exact figures for the prevalence of both HVI and HVE. It is considered to be approximately 0.8 per 100 000 population [1-3]. Despite being an important public health problem, very few population-based studies have been carried out so far in the world and none in Ukraine. We present the clinical and etiological data obtained in prospective single center population study with 107 enrolled adult patients in Ukraine.

The aim of this study was to better define the clinical profiles and etiologic priorities of HVE in Ukraine through a prospective hospital-based study from January 2014 to January 2015.

2. METHODS

2.1 Study Design, Patients and Site

This prospective study examining the correct HVs that cause encephalitis, took place from January 2014 until the end of December 2014at The Center of Infectious Disorders of the Nervous System (Kyiv, Ukraine). CIDNS is an adult tertiary referral, infectious diseases hospital covering Kyiv and the central regions. It has 20 beds with approximately 200-250 admissions annually. Patients are admitted to CIDNSif they have clinical evidence of a CNS infection: fever >38℃, or febrile episode reported within the previous month; cerebrospinal fluid (CSF) abnormalities (>four white blood cells per mm^3 or CSF proteins >0.4 g/L); at least one of the neurological signs (confusion, altered mental status, seizures, focal deficiency). Exclusion criteria included noninfectious CNS disease (cerebral tumor, cerebral abscess, and neurosurgery within the previous two-four months) and meningitis without clinical manifestation of brain involvement. Patients below 18 years were not included in the study, since children with CNS infections are managed in other specialized centers.

Basic demographic information was collected from all patients using case report forms. Patients were managed by hospital doctors following routine clinical practice i.e. history, physical examination, haematology, biochemistry, blood and CSF culture, and lumbar punctures (LP), and radiology. The CSF and serum samples were collected from all patients at admission and immediately sent to lab for analysis.

2.2 Vaccine Status

According to the Order of the Ministry of Health of Ukraine No. 276 of October 31, 2000,

mandatory preventive vaccinations are conducted against the following infections: Hepatitis B, Tuberculosis, Diphtheria, Pertussis (Whooping cough), Tetanus, Poliomyelitis, Measles, Rubella, epidemic Parotitis. No regular antiherpetic vaccines are currently used in Ukraine.

2.3 Serology

Enzyme Linked Immunosorbent Assay(ELISA) test (Euroimmun AG, Germany) was used for serological survey. The diagnostic algorithm included testing for antibodies of class M to herpes simplex virus1/2 (HSV1/2),cytomegalovirus(CMV), Epstein Barr virus (EBV), varicella zoster virus (VZV), and class G tohuman herpesvirus (HHV) 1-6, and autoantibodies to the main protein of myelin, S-100, neurospecific enolase (NSE), the general human brain antigen. All patients were tested for the above markers.

2.3.1 Intrathecal antibody (ITAB)

Intrathecal antibody (ITAB) synthesis to any HVs, one of the inclusion criteria of this study, was determined by the standard method used at our laboratory [4,5]. Briefly, we calculated the serum/CSF sample ratio by measuring the IgG titers of the specific virus by ELISA, where after this ratio was compared with the ratio of corresponding IgG titers against a reference virus (for example, measles, or another antigen). In addition, the CSF/serum albumin ratio and IgG index, (CSF/serum IgG ratio)/ (CSF/serum albumin ratio), were calculated to estimate blood-brain barrier damage and intrathecal antibody production [6].

2.4 Real-time PCR Analysis

The qualitative and quantitative content of viral DNA in CSF and blood samples was determined in the commercial laboratory “DNA lab” (Kiev) using kits for detection and quantification of Human Herpesvirus DNA by Real-Time PCR from ABAnalitika, and ABI 7500 Fast Dx cycler. The limit of the analytical sensitivity for the kit (p = 0.05) with ABI 7500 system is 0.4 – 2 viral genome copies (gc) / µL DNA extract (depending on specific virus), the linear range is 2.5 to 107 gc / reaction. Thus, the resultswere available in digital form as an exact DNA concentration in 1 ml of the sample. Electrophoresis of real time polymerase chain reaction (rt-PCR) products according to the reaction procedure was not provided.

2.5 Clinical Diagnosis and Final Decision

The final conclusion for the etiology of infection and recruiting the patient into the study was mainly based on the detection of viral DNA in CSF or blood, however neuroimaging data and characteristic clinical signs also were taken into account. The diagnosis was considered to be Confirmed when the DNA of any pathogen was found by PCR in the CSF (or blood) samples; Highly probable - when intrathecal IgG antibody synthesis against a specific virus and/or IgM AB in blood were detected; Suspected – when only IgG antibodies were found in the blood [7]. Patients of the first two group were enrolled into the study.

Written inform consent was obtained from all patients or from close relatives.

2.6 Statistical Analysis

For statistical analysis continuous data were compared with Mann-Whitney *U* test. Proportions were analyzed by Fisher’s exact test. A *p* value of ≤0.05 was considered statistically significant.

3. RESULTS

3.1 Demography

Altogether 196 patients meeting the initial criteria of CNS infectious disorders were enrolled between January 2014 and January 2015. The majority of patients admitted to CIDNS were transferred from another hospital. Altogether 89 patients were excluded from further analysis because the diseases were caused by bacteria or non-infectious in nature. The remaining 107 adult patients with confirmed herpesvirus infection and symptoms of possible encephalitis (CNS lesion) were analyzed in the study. A total of 33 (30.8%) patients were males, and 74 (69.3%) – females, the male to female ratio was 1:2.2. The median age of patients was 36.9 years (range 20-65 years). The demographic and clinical characteristics of the participants are outlined in Table 1.

3.2 Clinical Features

Preadmission illnesses lasted a median of 52 days, range 11 to 188. Clinical profiles observed among the patients with herpesvirus in CSF are

characterized by extreme diversity and a combination of several CNS symptoms and syndromes. The symptoms of the patients on admission are presented by frequency in Table 1. Overall, headache 93 (86.9%) and cochlea-vestibular impairments 88 (82.2%) were the most commonly recorded symptoms. Vegetative dysfunction 45 (42%), fever 9 (8.4%), sleep disorders 8 (7.5%), mental confusion 13 (12.1%), pyramidal insufficiencies 38 (35.5%), convulsions 32 (29.9%), scattered neurological symptoms 29 (27.1%), pelvic disorders 6 (5.6%), reduced hearing 6 (5.6%) were reported less frequently. A minority of patients had neurological signs e.g. nerve palsies/paresis 8 (7.4%). Profound hearing loss was not detected.

Table 1. Demographic characteristics of the study participants

Number of patients	**107 (100%)**
Age, Me (range)	**36.9 (20–65)**
≤ 20 years	4 (3.73%)
21–30 years	33 (30.84%)
31–40 years	28 (27.8%)
41–50 years	25 (26.16%)
51-60 years	14 (13.1%)
≥ 61	3 (2.8%)
Male	33 (30.8%)
Female	74 (69.3%)

3.3 CSF and Blood Profile

The majority of patients 103 (96.2%) hadlumbar punctures (LPs) done either on admission (n=88, 82.2%) or by the next day. White cell count (WCC) in 71% of CSF samples was < 10 cells/mm^3. In the remaining samples, moderate cytosis was observed. Lymphocyte prevailed. The protein content of CSF was normal in 89 (83.2%) patients, and slightly increased (up to 0.99 g / l) in 18 patients.

Normal level of WBC, or a small leukopenia was recorded in the blood.

The genome of HVs was detected in CSF samples obtained from all patients as follows: *Herpes simplex virus 1 and 2*– 13 (12.1%), *Varicella zoster virus*– 2 (1.8), *Cytomegalovirus*– 14 (13%), *Epstein Barrvirus*– 22 (20.5%), *Human herpesvirus 6*– 5 (4.7%), *Human herpesvirus 7*– 13 (12.1%). Co-infection (≥ 2 HVs) was observed in 38 patients (35.5%). CSF of 27 patients contained two viral DNA, and 11 – three one in various combination. Human herpesvirus 8 was not found.

Table 2. Summary of clinical features, laboratory, and radiology data

	Patients (n=107/100%)
Clinical signs	
Fever	98 / 8.4
Meningism (stiff neck)	46 / 43
Decreased level of consciousness	2 / 1.9
Disorientation	8 / 7.5
Confusion	81 / 75.7
Seizures	17 / 15.9
Focal neurological sings	92 / 86
Speech disorders	1 / 0.9
Cranial nerve palsy	24 / 22.4
Cerebellous syndrome	31 / 29
Sensory disorders	12 / 11.2
Myelitis	17 / 15.9
Aggressiveness	2 / 1.9
Apathy	86 / 80.4
Agitation	15 / 14
Parkinsonism	2 / 1.9
Hallucination	3 / 2.8
White cell count in CSF	
Normal (≤10/mm^3)	76 / 71
10-1000 mm^3)	31 / 29
Predominance of PMNs	7 / 6.5
Predominance of lymphocytes	100 / 93.5
CSF protein	
Normal (0.15-0.35 g/L)	89 / 83.2
Elevated (>0.35 g/L)	18 / 16.8
CSF/serum glucose ratio	
Normal (>0.4)	104 / 97.2
Low (≤0.4)	3 / 2.8
Typical infectious pattern	
Bacterial [a]	15 / 14
Viral [b]	92 / 86
Viral DNA in CSF and/or blood	
HSV-1/2	13 / 12.1
VZV	2 / 1.8
CMV	14 / 13
EBV	22 / 20.5
HHV-6	5 / 4.7
HHV-7	13 / 12.1
Mixt infection	38 / 35.5
Neuroimaging (MRI data)	
Focal lesions	61 / 57
Diffuse lesions	35 / 32.7
W/o changes	11 / 10.3
Outcomes	
Complete recovery	55 / 51.4
Improvement	49 / 45.8
Deterioration	3 / 2.8
Sequelae	0
Death	0

[a] Typical bacterial infections pattern: WBC count >100/mm^3, predominance of PMNs, mild to marked elevation of protein, normal to marked decrease of CSF/serum glucose ratio.
[b] Typical viral infections pattern: WBC count ≤100/mm^3, predominance of lymphocytes, normal to elevated protein, normal CSF/serum glucose ratio

3.4 Imaging

An important diagnostic and prognostic value has also neurovascular changes in the structure of the brain (Table 2, Figs. 1-4). As can be seen from the table focal changes in the brain are observed more often - in 61 (57%) cases against 35 (32.7%) for diffuse disorders. In 11 patients (10.3%) no changes in MRI were detected.

Findings include focal and diffuse changes of the limbic system around bilateral, temporal, occipital, and frontal areas. Signs develop gradually, but are somewhat delayed as compared to the clinical symptoms. Encephalitis often involves the cortex, hippocampal, and extrahippocampal structures involving the amygdala, tentorial cortex, thalamus, hypothalamus and deep forebrain structures, cerebellum, and brain stem (Figs. 1-4). Edema, necrosis, and sclerosis are frequently found. These typical findings are subsequently resolved and brain atrophy is observed in the convalescent period.

Taking into account the localization of CNS lesions, the following clinical diagnoses were established: Arachnoencephalitis, encephalitis, and meningoencephalitis – 46 (43%), arachnoiditis – 34 (31.8%), disseminated encephalomyelitis – 16 (15%).

3.5 Treatment

Patients with approved neurological symptoms received Acyclovir (20 mg/kg), which was administered intravenous daily during 2-3 weeks to all patients with HSV-1/2 and VZV infections), or Ganciclovir (10 mg/kg, per day intravenous for 2-3 weeks to patients with EBV, CMV, HHV-6, and HHV-7 infections). Interferon α2b 3000000 IU per day for 2 weeks, or human immunoglobulin intravenous (0.2 g/kg per day for 5 day) and managed supportively with ademetionine, 400 mg, and citicoline, 1000 mg both intravenous daily.

3.6 Outcome

The mean duration of hospital stay was 19.7 ± 15.3 days (range: 7-69). As a result of treatment, 55 patients had a good outcome and after discharge they returned home. The condition of 49 patients improved significantly (a decrease of some neurologic symptoms, but with preservation of some manifestations of cerebrosthenic, vestibulo-atactic syndromes, pyramidal insufficiency). These patients were transferred to a convalescence facility. Three patients, which condition worsened against the background of the therapy (dysfunction of the stem and cortical structures increased), were moved to an intensive care unit for further treatment. No patient died.

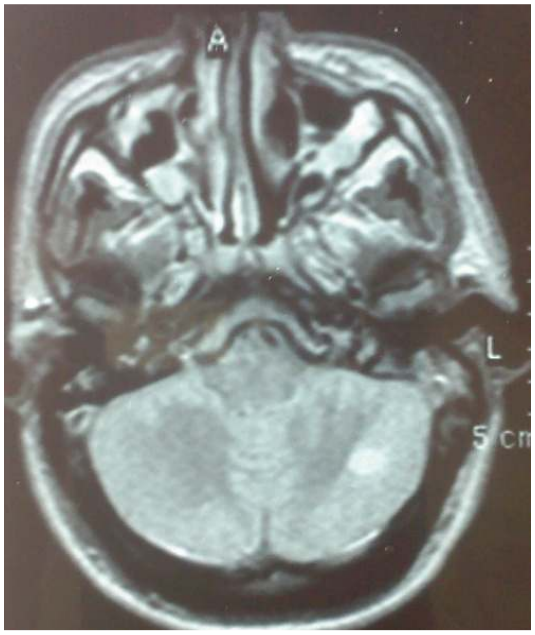

Fig. 1. HHV-7 encephalitis with cerebellar lesion

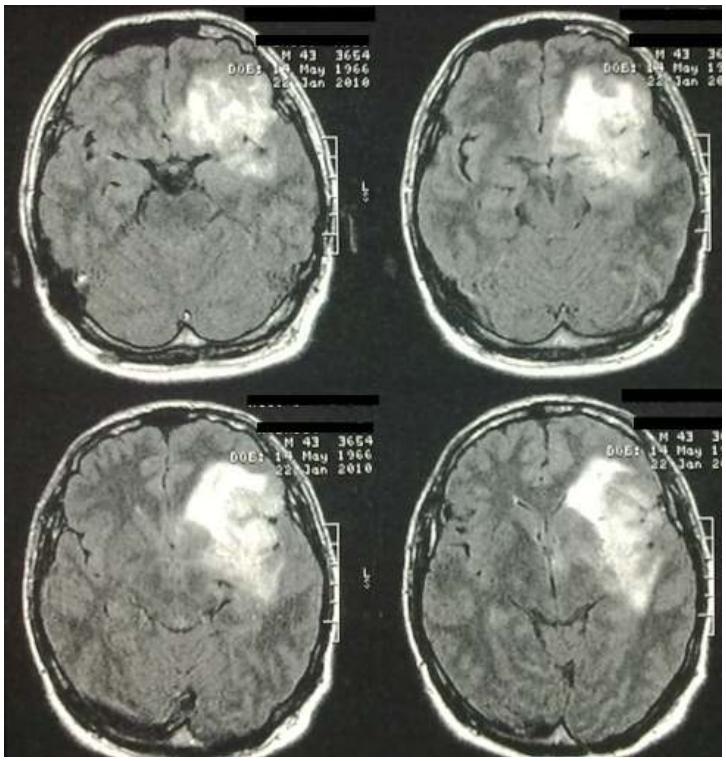

Fig. 2. Encephalitis with focal lesions in the left frontal-temporal lobe, associated with HSV-1/2 + EBV co-infection

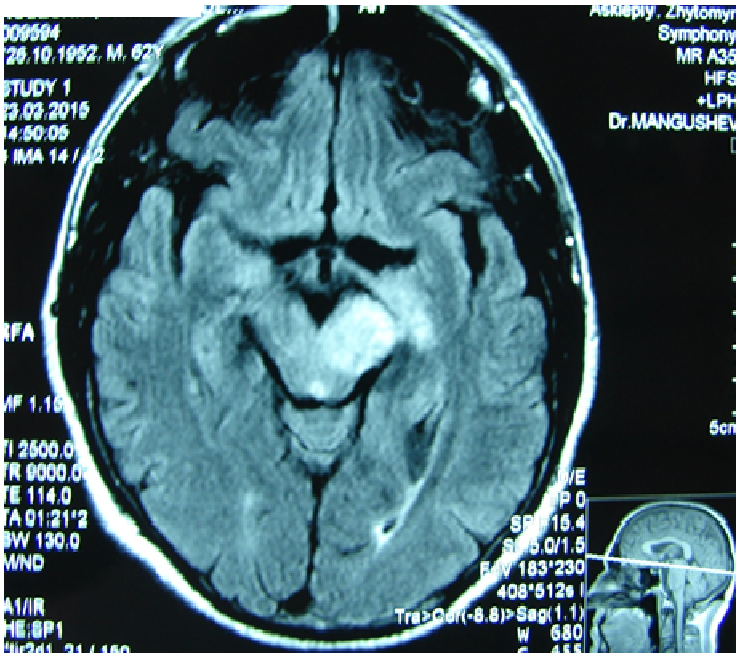

Fig. 3. Brainstem encephalitis associated withCMV + HHV-6 co-infection

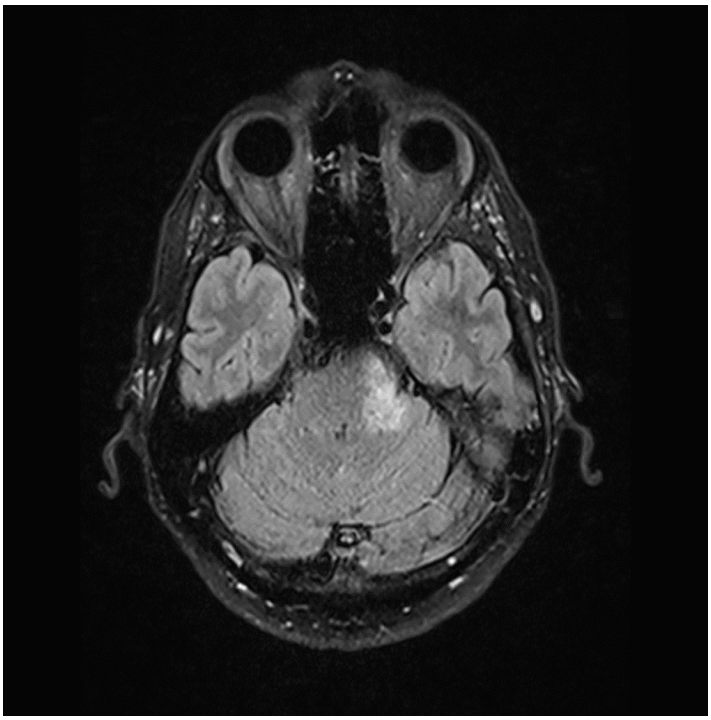

Fig. 4. EBV-associated encephalitis with lesion of brainstem and cerebellum structures

4. DISCUSSION

This prospective study has documented the range of herpesviruses causing CNS infections in patients admitted to a referral hospital in Kyiv. The data described here highlight the main clinical characteristics of herpesvirus associated encephalitis and other lesions of CNS. Should first emphasize the unnatural gender ratio of patients with a large prevalence of women. Of course, there is a sex balance in the general population, but this really reflects the gender composition of patients on hospital treatment. For example, in our center, seven out of eight hospital wards are reserved for women.

The clinical and etiological diversity of herpesvirus infections makes diagnosis difficult, although it is clear that the identification of an infectious agent is critically important, not only for establishing an accurate diagnosis, but also for the timely administration of specific treatment [8]. Diagnostic procedures include serological responses to specific antibodies in the blood and cerebrospinal fluid (CSF), the detection of pathogens by molecular methods in CSF and blood, and sometimes even cultivation of pathogens in culture [9]. The diagnosis is verified through epidemiological data and clinical symptoms, among which fever, headache, altered consciousness, seizures, routine CSF analyzes and neuroimaging [9]. Despite all diagnostic achievements, the etiologic cause of much of the cases remains unknown. Thus, in the California encephalitic project, in which 1570 patients took part, 63% had no encephalitis cause [11]. In a similar French study, the cause of the disease remained unknown in 80% of cases [10]. The high incidence of an unidentified diagnosis is partly due to the lack of sensitivity and specificity of the diagnostic methods currently used in the clinic [8,11]. An analysis of cerebrospinal fluid (CSF) in sporadic E typically exhibits lymphocytic pleocytosis at normal levels of glucose and protein, but often normal indicators can be observed only at the onset of the disease [12]. In CSF, a small number of erythrocytes is sometimes found, which reflects the potentially hemorrhagic nature of the disease [13]. In this study the opening pressure was sometimes elevated, and a CSF cytosis was not exceed 10 cells/mm^3 in over 70% of our patients. The cells were predominantly lymphocytes with a mean of 20 cells/mm^3 (0.02×10^9 cells/l). CSF protein levels, andCSF/glucose ratiowere bothmainly normal. Increased CSF antibody to specific herpesvirus, and a reduced serum/CSF antibody ratio, might help to diagnose HVE. According to the literature data, intrathecal antibody detection in the CSF HVE is strong

evidence for etiology [14]. On the contrary, systemic serological responses should not be considered for diagnosis. However, the data we have obtained indicate that the interpretation must be very cautious. So, very often antibodies for virtually all HVs were found in the CSF. Such false positive results appear most likely due to the cross reactivity of the ELISA kits used. Therefore, positive results were taken into account only in case of coincidence with PCR data.

The use of DNA analyses enhanced substantially our ability to diagnose patients. Indeed, PCR was the only diagnostic tool in our setting for viral pathogens. Timely made diagnosis allowed appropriate treatment to be given. PCR detection of pathogen DNA in CSF is sensitive and specific, and has become the diagnostic procedure of choice, although PCR results can be negative during the early stages of disease [15].

The results obtained in this study were, in general, in line with a number of previous studies, but in some details Ukrainian priorities differ from the word: the most prominent cause of HVE in our patients was EBV (20%, $p<0.05$)), followed by HSV-1/2, CMV and HHV-7 (each on 12-13%). Similarly, high prevalence of HSV-1/2, and some less CMV was shown in previously published results [1-3]. In Poland, about a quarter of all CNS infections are caused by HSV-1 [16]. In Brazil, 200 patients with CNS infections were analyzed. Herpesvirus DNA was detected in 12% of CSF, distributed as follows: 6% CMV; 5% HSV-1; 05% EBV and VZV one each [17]. A high EBV prevalence in patients with encephalitis (16 out of 23 cases) was found in study conducted in Taiwan [Hsu et al., 2013]. The result is similar to those shown here. Italian researches found the genome of herpesvirus in 33.5% (52/155) of patients with acute neurological disorders. VZV was detected in 30.9% cases followed by HSV-1 (27.9%), and coinfection (25.4%). The last figure is very similar to our study [18]. On the other hand, the VZV is considered to become the second most common herpetic causative agent of CNS lesions in the world, which is at the end of the list in this study [19,20]. Indian group shown immusupression sharply increased the number of cases with combined infections: a single virus was detected in 20 out of 45 HIV-infected persons, 19 cases were co-infected with two viruses, and 6 cases were positive for the three viruses [21].

In the same time, some researchers indicate a decrease in clinical and laboratory manifestations of herpesvirus infections of the CNS. In their opinion, a high fever became less frequent, and the content of cells and protein in the liquor remain normal more often [22].

In the correct diagnosis of CNS infections neuroimaging becomes key. The instrument of neuroimaging can be computed tomography (CT), preferably with contrast, or MRI. From our point of view, MRI is better suited for the diagnosis of encephalitis due to higher resolving capacity than CT. The absence of changes in MRI does not exclude CNS lesions, especially in the early stages of the infection, so it should be repeated 4-7 days if suspicion remains [23]. Thus, in one study, in 25% of patients with clinically and biologically diagnosed HVE, no pathological changes were detected [24].

This study had some limitations; one was the non-inclusion of other viral agents such as enterovirus, adenovirus and arbovirus that are known to be responsible for similar neurological symptoms. Additionally, herpes simplex virus was not subtyped.

5. CONCLUSION

It was the first epidemiological surveillance of herpes encephalitis in Ukraine. The findings contribute to understand the epidemiology of encephalitis and the clinical management of patients. Furthermore, this study described the main clinical manifestations of the disease, its evolution, and the use of antiviral agents in the adult population.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, et al. Causes of encephalitis and differences in their clinical presentations in England: A multicentre, population-based prospective study. Lancet Infect Dis. 2010;10(12):835-844.
   PMID: 20952256
   DOI: 10.1016/S1473-3099(10)70222-X
2. Kaeley N, Bansal S, Bhatia R, Ahmad S. Herpes simplex encephalitis: An uncommon presentation. J Clin Diagn Res. 2016;10(5):25-26.
   DOI: 10.7860/JCDR/2016/19040.7801
   Epub 2016 May 1
3. Mailles A. Infectious encephalitis in France in 2007: A national prospective study. Clin Infect Dis. 2009;49:1838–47.
   DOI: 10.1086/648419
   PMID: 19929384
4. Reiber H, Lange P. Quantificationof virus-specific antibodies in cerebrospinal fluid and serum: Sensitive and specific detection of antibody synthesis in brain. Clin Chem. 1991;37(7):1153-1160.
5. Denes E, Labach C, Duroxa H, et al. Intrathecal synthesis of specific antibodies as a marker of herpes simplex encephalitis in patients with negative PCR. Swiss Med Wkly. 2010;140:w13107.
6. Linde A, Klapper PE, Monteyne P, Echevarria JM, Cinque P, et al. Specific diagnostic methods for herpesvirus infections of the central nervous system: A consensus review by the European Union concerted action on virus meningitis and encephalitis. Clin Diagn Virol. 1997;8:83–104.
7. Horwood PF, Duong V, Laurent D, Mey C, Sothy H, Santy K, et al. Aetiology of acute meningoencephalitis in Cambodian children, 2010–2013. Emerging Microbes & Infections. 2017;6:e35.
   DOI: 10.1038/emi.2017.15
8. Studahl M, Lindquist L, Eriksson BM, Gunther G, Bengner M, Franzen-Rohl E, et al. Acute viral infections of the central nervous system in immunocompetent adults: Diagnosis and management. Drugs. 2013;73:131–158.
9. Solomon T, Hart IJ, Beeching NJ. Viral encephalitis: A clinician's guide. Pract Neurol. 2007;7:288–305.
10. Mailles A, Vaillant V, Stahl JP. Infectious encephalitis in France from 2000 to 2002: The hospital database is a valuable but limited source of information for epidemiological studies. Med Mal Infect. 2007;37:95-102.
11. Glaser CA, Honarmand S, Anderson LJ, Schnurr DP, Forghani B, Cossen CK, et al. Beyond viruses: Clinical profiles and etiologies associated with encephalitis. Clin Infect Dis. 2006;43:1565-77.
12. Baringer JR. Herpes simplex. Neurol Clin. 2008;26:657-74.
    DOI: 10.1016/j.ncl.2008.03.005
13. Whitley RJ, Soong SJ, Linneman C, Liu C, Pazin G, Alford CA. Herpes simplex encephalitis. Clinical Assessment. JAMA. 1982;247:317-20.
    DOI: 10.1001/jama.1982.03320280037026
14. Ongrádi J, Ablashi DV, Yoshikawa T, Stercz B, Ogata M. Roseolovirus-associated encephalitis in immuno-competent and immunocompromised individuals. J Neurovirol. 2017;23:1–19.
    DOI: 10.1007/s13365-016-0473-0
15. Tique V, Mattar S, Freire M, Illian E, Camargo F, Vergara O, et al. Epidemiological surveillance of herpes viral encephalitis in Cordoba, Colombia. Rev Salud Pública. 2016;18(4):581-591.
    DOI: 10.15446/rsap.v18n4.47517
16. Gilden DH, Mahalingam R, Cohrs RJ, Tyler KL. Herpesvirus infections of the nervous system. Nature Clin Pract Neurol. 2007;3(2):82-94.
17. Mendoza LP, Bronzoni RV, Takayanagui OM, Aquino VH, Moraes-Figueiredo LT. Viral infections of the central nervous system in Brazil. J Infect. 2007;54(6):589-96.
18. Gaeta A, Verzaro S, Cristina LM, Mancini C, Nazzari C. Diagnosis of neurological herpesvirus infections: Real time PCR in cerebral spinal fluid analysis. New Microbiol. 2009;32(4):333-340.
19. Becerra JC, Sieber R, Martinetti G, Costa ST, Meylan P, Bernasconi E. Infection of the central nervous system caused by varicella zoster virus reactivation: A retrospective case series study. Int J Infect Dis. 2013;17(7):e529-34.
20. Pollak L, Dovrat S, Book M, Mendelson E, Weinberger M. Varicella zoster vs. herpes simplex meningoencephalitis in the PCR era. A single center study. J Neurol Sci. 2012;314(1-2):29-36.
21. Kannangai R, Sachithanandham J, Mahadevan A, Abraham AM, Sridharan G,

Desai A, et al. Association of neurotropic viruses in HIV-infected individuals who died of secondary complications of tuberculosis, cryptococcosis, or toxoplasmosis in South India. J Clin Microbiol. 2013;51(3):1022-1025.

22. Barker KR, Sarafino-Wani R, Khanom A, Griffiths PD, Jacobs MG, Webster DP. Encephalitis in an immunocompetent man. J Clin Virol. 2014;59(1):1-3.

23. Höllinger P, Matter L, Sturzenegger M. Normal MRI findings in herpes simplex virus encephalitis. J Neurol. 2000;247:799-801.
DOI: 10.1007/PL00007798

24. Wasay M, Mekan SF, Khelaeni B, Saeed Z, Hassan A, Cheema Z, et al. Extra temporal involvement in herpes simplex encephalitis. Eur J Neurol. 2005;12:475-9.
DOI: 10.1111/j.1468-1331.2005.00999.x

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/20397