CLINICAL CASE OF MULTIPLE SCLEROSIS ASSOCIATING WITH PERSISTENT HERPES VIRUS INFECTION: DYNAMICS ON THE BACKGROUND OF ANTIVIRAL AND IMMUNOCORRECTIVE TREATMENT

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Abbreviation

Circulating immune complexes (CIC); Central nervous system (CNS); Epstein – Barr virus (EBV); Human herpesvirus 6 (HH6); Herpes simplex virus 1 (HS1) ; Immunofluorescence coefficient (Ic); Magnetic resonance imaging (MRI); Multiple sclerosis (MS); Optical density units (Op.d.u); Peripheral blood mononuclear cell (PBMCs); Varicella – Zoster virus (VZV)

Introduction

Several lines of evidence suggest that multiple sclerosis (MS), like other autoimmune diseases, may be triggered by microbial infections [1]. Pathogens associated with development or exacerbation of MS include bacteria, such as Chlamydia pneumoniae, Staphylococcus aureus-produced enterotoxins that function as super antigens, and viruses of the Herpesviridae (Epstein-Barr virus, human herpes virus 6 and others) and human endogenous retrovirus families. However, to date, no single pathogen has been accepted as causal agent [2]. Viral aetiology has been suspected to be an MS trigger for a long time, and herpesviruses are among the potential pathogens involved. The more we understand the mechanisms of MS pathogenesis, the clearer it becomes that this disease is a truly multifactorial problem with genetic, external, and immunological components [1-3]. The extent of interplay between these different factors is under rigorous investigation [4, 5].

MS pathology is characterized by two major hallmarks: inflammation and progressive neuroaxonal damage [6-8]. The main mechanisms of virus participation in MS pathogenesis may by direct damaging of active viral infection in the central nervous system cells, complexity of genetically viral interaction, molecular mimicry, when some pathogen proteins have homologous aminoacid sequences with self-proteins and is possible mechanism viral-induced autoimmune response, bystander activation and epitope spreading [6]. The clinical heterogeneity of MS and the diversity of MS lesions in the CNS suggests that the disease is not caused only by a single virus, but rather by a complex of viral infections that can act as triggers in genetically susceptible individuals [7].

Herpes viruses are neurotropic, but also neurovirulent i.e. they can infect CNS cells, and also cause CNS disease [2, 8]. Although it is possible that a virus triggering MS directly lyses cells in the CNS, it is more likely that MS is associated with an immunopathogenic host-immune response to the virus [3, 9]. In recent years, there are more references have become increasingly frequent in the literature about herpes detection MS lesions in brain and serological evidence of the presence and activity this viruses in MS patients and also the positive effect of antiviral treatment [5]. However, not so many studies have been conducted for the immunomodulators and biologically active agents. Main focus in MS treatment was and remains for immunosuppressive therapy [10]. Although, the use of interferon β has shown a positive trend in the patients' condition, in recent years there has been return to drugs that suppress the immune response and the search and clinical trials of new selective immunosuppressants [11-14]. There are enough publications about the risks of activation the opportunistic infections during these drugs treatment [12-15]. We would like to initiate research on immunecorrective drugs for MS treatment [10-13]. This trend is promising in the light of infectious nature MS development and autoimmune mechanisms understanding as consequence of the viruses activity.

Clinical case

Patient N., female, 35 years old, was diagnosed with multiple sclerosis, disseminated, relapsing remitting, exacerbation stage with moderately expressed right-sided paraparesis, with motor and sphincter disorders, pronounced vestibule-ataxic (vestibulocerebellar) syndrome, cognitive impairment, EDSS 4.5–5.0 in 2013. A brain and spine MRI showed numerous bilateral hyperintense T1 (7 without gadolinium and 10 with gadolinium), and several (5) T2 lesions and FLAIR contrast-enhancing over the hemispheres and cerebellum and several (6) T1, (4) T2 lesion in her cervical spinal cord sizes from 0.3 cm to 1.1x0.6x1.1 cm individual foci with signs of perifocal edema. At the time of diagnosis complaints of dizziness, shakiness when walking, weakness and a feeling of numbness in the limbs, discoordination of movements, impaired urination by the type of delay with frequent urges, decreased performance, fatigue, unstable gait, muscle cramps, decreased muscle strength (4), slight speech disturbances, depression and anxiety. She treated with pulses of corticosteroids (1.5 g methylprednisolone) with gradual tapering of the steroids over a period of 4 weeks and plasmapheresis according to standard treatment.

The first symptoms appeared 6 months before the diagnosis was established and gradually increased. Complaints were preceded by an episode of acute viral infection and prolonged low-grade fever for 3 months.

After carrying out the standard basic therapy with corticosteroids, her condition worsened, and the patient refused for several years from the proposed therapy. In 2017 she came to Medical Center “Your Family” for consulting with significant impairment motor activity and sensitivity right half of the body, severe weakness, decreased performance, paroxysmal headache, thinking delays and speech disorders, and violation of writing.

The patient received treatment and consulted by a neurologist and immunologist.

Neurological status: The eye slits are even, the movements of the eyeballs are full, painless. Nystagmus horizontal in extreme leads, more when looking to the left. Pupils D=S. Diplopia. The photoreaction is alive. The face is symmetrical. Middle tongue. The language and swallowing are not affected. The tendon hands` reflexes D<S are high with the extension of the reflexogenic zones, feet D=S reduced. Muscular tone with a tendency to under-spasticity in the lower extremities. Muscle strength from the right extremities 3-3.5, from the left extremities 4. In the Romberg`s pose slightly staggered. The gait is somewhat atactic.

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The patient was examined and treated according to the national protocols of multiple sclerosis [17] – supportive therapy milgamma, thiogamma, metamax, noophen, neiromidinum prescribed courses 2 times per year, without corticosteroids, due to worsening after the previous treatment. Therefore, due to the lack of medical insurance and financial ability of patients, it was not possible to use expensive β-interferons, copaxone and selective immunosuppressants monoclonal antibodies. Immunological and antiviral treatment was prescribed based on patient`s laboratory data and taking into account modern scientific research.

From the anamnesis it is known that the patient was sick varicella (chickenpox) at the age of 8 years with the usual course. Also 2-3 times a year over the past 10 years, colds have been accompanied by Herpes labialis.

Serum antibodies and antigen herpes viruses screened using the following methods: virus-specific IgM and IgG antibodies HSV 1, VZV, EBV (early antigen EA, against viral capsid antigen VCA, EBV nuclear antigen EBNA), HH6 by commercial enzyme-linked immunosorbent assay (ELISA) and viral load in PBMCs by immunofluorescence. No Ig M detected. Positive IgG to HSV 1, VZV, VCA, EBNA and HH6 found. The patient was assessed immune status and viral load in PBMCs (peripheral blood mononuclear cells) using immunofluorescence for herpes viruses HS1, VZV, EBV, HH6. At the first examination high viral load detected in PBMCs (EBV 1.6; HH6 1.7; HS1 1.3; VZV 1.4, respectively). In the study of the immune status observed: absolute and relative lymphocytosis, an increased number of lymphocytotoxic autoantibodies and circulating immune complexes, an increase in CD3, CD8, and NK cells, a decrease in the complement system CH50.

Based on these analyzes next treatment administered: valacyclovirum 3000 mg per day, recombinant interferons α2b at dose 1000,000 IU per day and cridanimodum (meglumine acridon acetate, a low molecular weight inducer of interferon synthesis) 1000 mg once a week intravenously. Additionally was recommended B1-thiamine mononitrate 200 mg, Ester-C 500 mg, D3-cholecalcferol 1000 IU, B12-methylcobalamin 1000 μg, E-alpha-tocopherol 400 IU, CoQ-10 100 mg per day.

After 30-days course of treatment the patient's condition assessed and follow-up studies were conducted. The frequency of attacks and the intensity of headache decreased by 2.3 times, increased efficiency, speech became clearer, gait somewhat more stable. As a result of the treatment appeared tendency towards stabilization of the immune status and approaching normal values. In the study of viral load in PBMCs was determined for EBV and HH6 with immunofluorescence coefficients 1.4 and 1.5, as well as for HS1 and VZV with coefficients 1.2 and 1.3.

Positive dynamics in the patient's state remained. We controlled viral load indicators every 30 days, the immune status every 90 days, an MRI performed every 6 months from the initiation of treatment for 2 years. Viral load changes periodically, in periods of significant decline antiviral and interferons treatment canceled, but cridanimodum used constantly. With an increase in viral load, valacyclovirum administered again. For 24 months, the patient underwent 12 monthly courses valacyclovirum.

The patient's condition improved after treatment: EDSS 3.0–3.5. Symptoms of unsteadiness in walking over the period of observation and treatment decreased, significantly increased working capacity, fatigue and dizziness, frequency paroxysmal neurological symptoms decreased, almost complete absence of paresthesia, fine motor skills recovered, tactile sensitivity improved. Neurological status: The eye slits are even, the movements of the eyeballs are full, painless. Nystagmus horizontal installation. Pupils D=S. The photoreaction is alive. The face is symmetrical. Middle tongue. The language and swallowing are not affected. The tendon hands` reflexes D=S are lively, feet D=S slightly reduced. Muscular tone with a tendency to under-spasticity in the lower extremities. Muscle strength from the right extremities 4-4.5, from the left extremities 5. There is slight instability in the Romberg`s position. The gait is a bit atactic.

MRI also showed positive dynamics: several small lesions in the brain disappeared, large MS lesions became smaller in size – T1 (3 without gadolinium and 8 with gadolinium), and T2 (5) over the hemispheres and cerebellum; T1 (4), T2 (3) lesion in her cervical spinal cord sizes from 0.3 cm to 0.7x0.4x0.8 cm, foci without signs of perifocal edema (Figure 1-3).

The patient's condition was noted stable improvement and reduced MS symptoms. Also positive changes observed in the immune status (Table 1).

Table 1. Changes in the immune status and viral load of the patient on the background of antiviral and immunocorrective treatment

Index	units	Before treatment	6 months immunocorrective and antiviral treatment	12 months immunocorrective and antiviral treatment	18 months Immunocorrective and antiviral treatment	24 months Immunocorrective and antiviral treatment
EBV	Ic	1,6	1,4	1,3	1,2	1,1
HH6	Ic	1,7	1,5	1,2	1,2	1,1
HS1	Ic	1,3	1,2	1,1	1,1	0,8
VZV	Ic	1,4	1,3	1,1	0,9	0,7
Lymphocytes	abs.	3312	3215	3180	3040	2700
CD 3+ T	abs.	1887	1832	1754	1637	1632
Lymphocytes	%	37	34	28	27	26
T - active	%	24	28	32	34	35
CD 4	abs.	1159	1121	1123	1080	987

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	%	35	32	31	33	28
CD 8	abs.	728	673	564	507	430
	%	22	21	22	20	18
0 - Lymphocytes	abs.	596	487	503	498	467
	%	18	18	17	18	16
CD 22 B - Lymphocytes	abs.	828	802	745	629	537
	%	25	25	23	22	20
CD 16 (NK)	%	11	10	13	12	12
CD 4/CD 8	u	1,59	1,46	1,58	1,6	1,64
Phagocytic index	%	69	67	64	65	64
Phagocytic number	u	3,7	4,0	3,9	4,1	4,1
CIC 3,5%, 7%	Op.d. u	0,07;0,078	0,07;0,074	0,069;0,070	0,063;0,065	0,06;0,062
Complement, CH50	u	29,6	31,2	33,0	34,2	35,5
Heterophilic hemolysins	Op.d. u	0,3	0,4	0,35	0,33	0,43
Lymphocyto toxic autoanti bodies	%	20	16	15	12	10

MRI showed decrease MS plaques over the observation period (Figure 1-3).

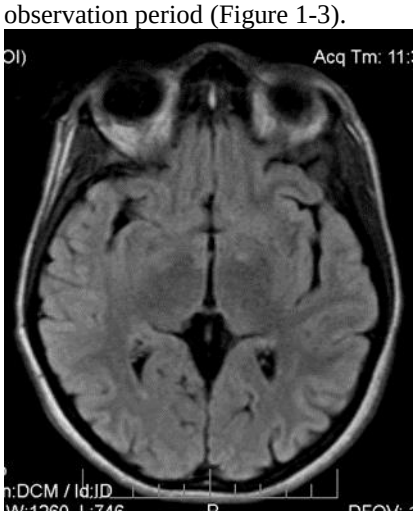

Figure 1. MRI 11.2017

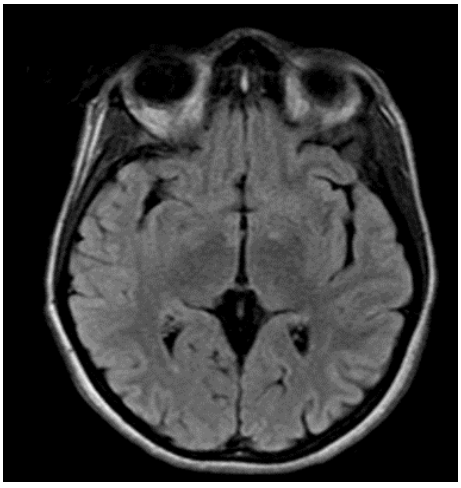
Figure 2. MRI 01.2018

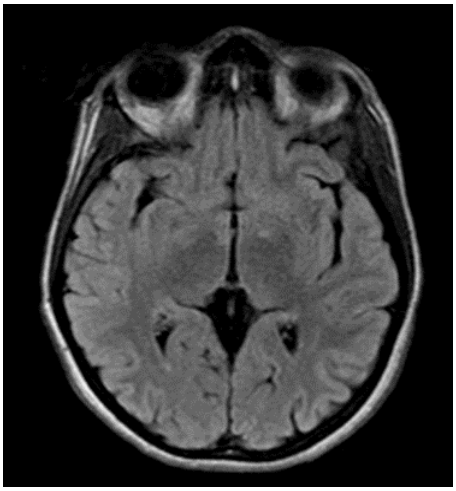
Figure 3. MRI 07.2018

Conclusions

Using the interferons, including alpha, which have a pronounced antiviral activity, as well as endogenous interferonogen is promising direction in MS treatment, which are basing on the viral theory of the pathogenesis this disease. In the clinical case, that we presented, first positive changes in the patient's condition observed in the initial stages of the drug using. Further enhancement of therapy with valacyclovirum in MS treatment allowed stabilization of immune parameters and contributed to decrease viral activity. Reasonable combination antiviral, immune and biologically-active drugs may be the key to solving some infectious-autoimmune problems, one of which is the MS. Therefore, the continuation of research and clinical observations in this direction should be considered promising. We are continuing research in this direction and are developing strategies for possible clinical trials of the complex examination and treatment in patients with MS.

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Clinical case of multiple sclerosis associating with persistent herpes virus infection: dynamics on the background of antiviral and immunocorrective treatment
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Rationale: Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system. Infectious triggers of MS are being actively investigated. Substantial evidence supports the involvement of the Epstein-Barr virus (EBV), though other viruses, bacteria, protists, and fungi are also being considered. For many years, researchers have discussed the relationship of demyelinating processes and development of multiple sclerosis (MS) associated with the activation and persistence of herpes viruses. In recent years, studies have increasingly proved the pathogenetic role herpes viruses in the development of this disease, but this requires further study. There is growing evidence that viruses can play a role by acting as external triggers. However, it is not known, one virus is the cause MS or several viruses can act as an impulse to the development the disease. **Clinical case:** Patient N., female, 35 years old, was diagnosed with multiple sclerosis, disseminated, relapsing remitting, exacerbation stage with moderately expressed right-sided paraparesis, with motor and sphincter disorders, pronounced vestibule-ataxic (vestibulocerebellar) syndrome, cognitive impairment, EDSS 4.5–5.0 in 2013. A brain and spine MRI showed numerous bilateral hyperintense (17) T1, and several (5) T2 lesions and FLAIR contrast-enhancing over the hemispheres and cerebellum and several (6) T1, (4) T2 lesion in her cervical spinal cord sizes from 0.3 cm to 1.1x0.6x1.1 cm individual foci with signs of perifocal edema. At the time of diagnosis complaints of dizziness, shakiness when walking, weakness and a feeling of numbness in the limbs, discoordination of movements, impaired urination by the type of delay with frequent urges, decreased performance, fatigue, unstable gait, muscle cramps, decreased muscle strength (4), slight speech disturbances, depression and anxiety. She treated with pulses of corticosteroids (1.5 g methylprednisolone) and plasmapheresis with gradual tapering of the steroids over a period of 4 weeks according to standard treatment protocols in the neurological department Kharkiv Regional Clinical Hospital. The first symptoms appeared 6 months before the diagnosis was established and gradually increased. Complaints were preceded by an episode of acute viral infection and prolonged low-grade fever for 3 months. We consider the clinical case patient with MS, it was detection the abnormalities in the immune status and viral load (herpes type 4 – Epstein-Barr virus, EBV and human herpes virus 6 – HH6), and positive dynamics was observed in condition of patient and MRI data after antiviral and immunocorrective therapy. **Interventions:** We administered valacyclovirum as the first therapy in combination with recombinant interferons α2b and cridanimodum. Additionally was recommended high doses of vitamins. **Outcomes:** The patient's condition improved after treatment: EDSS 3.0–3.5. MRI also showed positive dynamics: several small lesions in the brain disappeared, large MS lesions became smaller in size. (11) T1, and several (5) T2 over the hemispheres and cerebellum and FLAIR contrast-enhancing and several (4) T1, (3) T2

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lesion in her cervical spinal cord sizes from 0.3 cm to 0.7x0.4x0.8 cm individual foci without signs of perifocal edema. **Conclusion:** Early diagnosis and active antiviral and immunocorrective therapy is important when herpes are detecting in MS patients for treating and preventing further development of the disease, so we would like to highlight some aspects of the therapy carried out in this case for the perspective planning relevant clinical studies in the similar direction.

Keywords: Circulating immune complexes (CIC); Central nervous system (CNS); Epstein – Barr virus (EBV); Human herpesvirus 6 (HH6); Herpes simplex virus 1 (HS1) ; Immunofluorescence coefficient (Ic); Magnetic resonance imaging (MRI); Multiple sclerosis (MS); Optical density units (Op.d.u); Peripheral blood mononuclear cell (PBMCs); Varicella – Zoster virus (VZV)

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