



## Case report

# Apheresis Procedure could Prevent Sequele of Hsv1 Encephalitis – Case Report

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## Abstract

**Background:** Herpes simplex virus 1 is consistently the most common cause of sporadic encephalitis worldwide which leaves neurological deficits in more than 60% of survived patients. The immune response of a diseased person has a major impact not only on the course of the disease, but also on the response to the applied protocol, as well as the severity of brain damage. The proposed immunomodulatory therapy aims to restore the quality of the immune system, both innate and acquired to improve outcome of encephalitis.

**Case report:** Here we present case report of encephalitis treated according to the guidelines, who developed severe brain damage with consequent memory and cognition deficits as well as language disorders. In order to mitigate brain damage, our patient started apheresis protocol consisting of four sessions based on nanomembrane with four sessions of extracorporeal Laser blood irradiation, by red and infrared beams. Apheresis protocol was conducted in P. Pavlov First St. Petersburg State Medical University, Russia, on Hemophoenix device as minimally invasive and safe (plasma replacement with saline solution). The effect was such that the patient returned to full-time work five months after onset of encephalitis. MRI brain scan within six months after apheresis showed signs of good regression, but one year later defects was in good remission.

**Conclusion:** Apheresis procedure based on nanomembrane consist of four sessions, every other day, with extracorporeal Laser blood irradiation could mitigate sequelae of brain damage caused by herpes simplex virus 1 encephalitis.

## Introduction

Herpes simplex virus 1 (HSV1) is double-stranded DNA viruses which establish lifelong infection in humans. Although HSV1 is easily spread among individuals, it rarely causes death of the host. According to literature, HSV1 seropositivity among older adults estimated to be 60–90% worldwide [1].

HSV1 encephalitis (HSE) is consistently the most common cause of sporadic encephalitis worldwide [2]. Treatment with intravenous Acyclovir has decreased overall mortality from 70% to <20% [3]. Still, more than 60% of survivors will have neurological deficits, moderate to severe. Only 2–3% of HSE cases will survive with fully normal neurological function [4].

The pathogenesis of HSE is not clearly understood. Central Nervous System (CNS) cell damage induces direct action of HSV1 virus and host immune response activity. While many studies are beginning to implicate the immune response to HSV1 and its various cell population (e.g. microglia, CD8+T

cells) in causing widespread CNS pathology [5,6], the exact cause of the extensive destruction of CNS is still unclear [7]. Recently, researchers have pointed to significance of immune-mediated post-infectious HSE through identification of anti-N-methyl D-aspartate receptor (NMDAR) encephalitis as an autoimmune encephalitis [8].

Recently, the principles of Therapeutic Apheresis (TA) are gaining more and more attention given the rapid control of quantitative and qualitative abnormalities of plasma and/or blood components considering that pathological factors are separated from intravascular spaces. According to basic physiology, later the intravascular pathogenic factors enter the intracellular and interstitial space compartment. This requires several apheresis procedures at different intervals of time to achieve the optimal separation of etiopathogenetic factors of the disease or syndrome. Today, TA is used for treatment of more than 75 different diseases including viral [9].

TA on Hemophoenix device based on nanomembrane,



produced in Russia, was approved by American Society for Apheresis (ASFA) in 2013. as minimally invasive and safe because it is performed on a single needle and removed plasma is replenished only with saline solution [10]. Nanotechnological processes applied in membrane making have qualitatively improved the process of separation plasma proteins and human blood. More specifically, nanomembrane could “capture” the pathological antigens or antigen-antibody complexes, which would induce purification of the blood from disease-causing agents. The most frequently used replacement fluid is saline solution to avoid adverse complications even when 25% (approximately 700 – 750 ml) volume of the circulating plasma is separated [9].

In this paper, we aim to present a case report of the significant impact of a TA procedure consisting of four nanomembrane-based sessions on a Hemophoenix device in the prevention of neurological consequences in a patient suffering from HSE during the first 3 months of onset.

## Case report

A 54-year old man with no significant past medical history presented to the Emergency Department of the Clinical Center of Montenegro (CCM) due to fever and headache over past 3 days. In previous week the patient had a slightly elevated temperature up to 37.9°C and complained of mild frontal headache. His doctor treated him as maxillary sinusitis by antibiotic and antipyretic therapy. The day before hospital admission fever rised up to 39°C and he had short-term loss of consciousness in the sitting position that lasted no longer than 1 minute.

At hospital admission the patient was febrile (39.2°C) without neck stiffness or meningeal signs but chest-X ray pointed to suspect right consolidation, localised hilobasal and paracardial. Due to blood test results, white blood cells (WBC)12, neutrophils (NE) 75.5 % and C-reactive protein (CRP) 2.2 and physical examination, he was treated by dual antibiotic therapy (Ceftriaxone and Ciprofloxacin) at Infectious Clinic of CCM. In the next 2 days family members noticed decrease in the level of consciousness with fluctuations. CT brain scan was inconclusive with small reductive cortical changes, so lumbar puncture (LP) was ordered. In the cerebrospinal fluid (CSF) lymphocytic pleocytosis was confirmed (715 WBC of which 98% Ly) followed by Real Time - Polymerase chain reaction (RT-PCR) positivity to HSV1. Electroencephalography (EEG) has shown focal slowing cortical activity left in the frontotemporal areas. Additionally, MRI brain scan showed hyperintensity signal in left temporal lobe, hippocampus and frontal lobe in T2W1 sequences. According to guidelines for HSE treatment, he was receiving intravenous Acyclovir and symptomatic antiedematous therapy in the next 21 days. Control LP performed on the 12th day of treatment was RT-PCR negative for HSV1 but still presented lymphocytic pleocytosis (WBC 198, 95 % Ly).

Four days after the start of treatment the patient was afebrile, but the afebrile period lasts only 4 days, he was febrile again (38.2°C) regardless of the treatment. Simultaneously, begins to

develop significant cognitive deficits and language disorders. Due to the resulting deterioration 2 weeks after treatment onset, he was referred to Infectious Clinic in the Clinical Center of Serbia (CCS) for further treatment and additional diagnostic procedures. LPs were performed 2 times in the next 10 days and obtained results have pointed to a decrease of lymphocytic pleocytosis (first WBC 52, Ly 92 % and second WBC 49, Ly 94 %). MRI brain scan was ordered after completed treatment (21 days) and shown signal alteration zones in the left temporal lobe with engaging of amygdala-hippocampal and para-hippocampal regions, olfactory area, piriform cortex, insula and lateral occipito-temporal gyrus. Still, the patient every day was febrile. In mental status prominent memory deficits, especially retention of new informations, besides language disorders and altered cognition.

Additionally, serum and CSF NMDAR- antibodies were performed. Obtained results were negative in both samples. In the next 3 days, patient received pulse corticosteroid therapy and finally he was afebrile. So, after 49 days of hospital treatment he was discharged home as afebrile but with significant mental disorders.

MRI brain scan one month later, corresponds to the condition after HSE in the left temporal lobe basal including hypothalamus and basal frontal lobe to Sylvian fissure.

Thus, the patient was referred for TA to the specialized Clinic for Extracorporeal Hemocorrection, at the P. Pavlov First St. Petersburg State Medical University, Russia. The protocol was consisting of 4 session membrane apheresis based on nanotechnological produced membrane applied on Hemophoenix device. In each session plasma has been removed up to 800-900 ml, replaced only with saline solution in continuous infusion. Also, ACD-A or sodium citrate was used as anticoagulants. The whole blood was additionally extracorporeal irradiated with red and infrared Laser beams in every session. Sessions were made every other day. After finishing the whole protocol, the patient was significantly improved with regard to both physical as well as mental health. As a final result, the patient returns for full time work only 5 months after finishing hospital treatment of HSE.

Six months after finishing the TA protocol MRI brain scan indicated good regression and corresponds to the condition after HSE in left temporal lobe, basal. But, one year later MRI brain scan was in complete regression in left temporal lobe, basal with sequelae, gliosis and postencephalitic cyst 16.4 x 14.7 mm to cavernous sinus.

## Discussion

HSV1 is the most common cause of lethal sporadic encephalitis. Despite improved therapy with intravenous Acyclovir, HSE is associated with persistent severe neurological deficits [11]. So, it is understandable need to establish a diagnosis of HSE as early as possible in order to minimize sequelae that greatly impair quality of life. Fever and abnormal mental status are the primary signs and symptoms of HSE, occurring in >90% of patients [12]. In our case the first symptoms were fever and mental alteration which make him suspected for viral brain



infection. CT brain scan is not the imaging modality of choice in suspected viral encephalitis considering that abnormal findings have been observed in 25–80% of patients with HSE imaged soon after admission [13]. But normal CT brain scan cannot rule out the diagnosis [14]. The patient in our case had inconclusive finding of CT brain scan.

Clinical presentation and normal or inconclusive CT brain scan demand the next diagnostic step by performing a LP and CSF testing. Typical CSF profile in HSE includes moderate lymphocytic pleocytosis (10–200/mm<sup>3</sup>), may demonstrate elevated erythrocytes (normal minimally elevated counts are common), moderately elevated protein (50–100 mg/dL) and normal glucose [15]. According to literature, CSF analysis was abnormal in our case with remarkable high lymphocytic pleocytosis (715/mm<sup>3</sup>, 98%Ly).

RT PCR for HSV in CSF is the gold standard for the diagnosis of HSE and has high sensitivity (96%) and specificity (99%) [16]. Although, in our case RT PCR performed to a broader specter of pathogens, positivity was gained only for HSV-1. According to guidelines for HSE treatment the patients started with Acyclovir by scheme (10mg/kg body weight/8 h).

The current guidelines recommend intravenous Acyclovir for 14–21 days in HSE (17) in order to avoid immune mediated relapse. So, in our case patient received 21 days of Acyclovir. Even more, he has become RT-PCR negative for HSV1 in CSF within 14 therapy days. However, he begins to show signs of clinical relapse. He has fever again and worsening of mental status (depressed level of consciousness, confusion, memory lost, language difficulties). According to literature clinical relapse is not seldom but has been reported in range 5–27%. Many of these reported cases have no evidence of HSV1 activity in CSF (negative RT-PCR) and poor clinical response to antiviral medication [18]. For the most authors this was a proof that underlying mechanism is not mediated by direct viral cytotoxicity, but it is about immune mediated process. Lately, published studies that have demonstrate that many patients suffering HSE relapse develop autoimmune encephalitis known as anti-NMDAR [19,20]. Clinical presentation of anti-NMDAR encephalitis among other symptoms includes mental alteration such as progress of memory deficits and language disintegration [21]. In our case clinical relapse was not caused by producing antibodies to NMDAR since these antibodies were negative in serum and CSF. Further, our patient had a good response to pulse corticosteroid therapy which was one more proof of post-HSV-1 immune-mediated encephalitis.

Once viral reactivation or persistence have been excluded, treatment with immunomodulatory therapy should be strongly considered [8]. The first-line immunomodulatory treatment includes corticosteroids and/or intravenous immunoglobulins or plasma exchange. By Armague this treatment resulted in substantial improvement in all analyzed patients in the series [22]. In our case, the patient received only pulse corticosteroid therapy before being discharged from the hospital.

In conditions of immunosuppression because of the HSE treatment, it is necessary to correct the quality of the immune

response by improving its regulatory component in order to correct and re-establish immune and rheological response. Laser irradiation of blood during apheresis is aimed to restore energy homeostasis in the cells through reactivation of antioxidant protection as well as normalized erythrocyte rheological properties for improving tissue oxygenation. For this purpose, red and infra-red Laser beams are used as extracorporeal treatment through PVC blood lines. Published studies have shown that extracorporeal blood irradiation results in greater immunomodulatory and anti-inflammatory benefits characterized by activation of lymphocytes and macrophages, increased synthesis of IL-2, gamma-interferon, and beta2 microglobulin, in addition to improving microcirculation and tissue oxygenation [23].

The whole procedure consists of 4 sessions of membrane apheresis with extracorporeal Laser irradiation with red and infra-red beams in order to eliminate firstly pathological products from blood, later from interstitial body spaces and finally from cells.

In our case patient received whole procedure conducted on Hemophenix device which turned out to be a very effective for the best possible recovery. Primarily, the patient returns for full time work only 5 months after finishing hospital treatment of HSE. Even more, after one year his MRI brain scan shows good regression of post-inflammatory changes.

## Conclusion

HSV1 encephalitis as the most common sporadic encephalitis can cause serious neurological and mental disorders that severely impair quality of life. The apheresis procedure in combination with extracorporeal Laser blood irradiation could be a very effective therapeutic tool in the prevention of brain damage caused by HSV1 encephalitis.

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