Human herpesvirus DNA occurrence in intracranial aneurysmal wall: illustrative case

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BACKGROUND Subarachnoid hemorrhages secondary to intracranial aneurysms (IAs) are events of high mortality. These neurological vascular diseases arise from local and systemic inflammation that culminates in vessel wall changes. They may also have a possible relationship with chronic viral infections, such as human herpesvirus (HHV), and especially Epstein–Barr virus (EBV), which causes several medical conditions. This is the first description of the presence of HHV deoxyribonucleic acid (DNA) in a patient with IA.

OBSERVATIONS A 61-year-old woman with a downgraded level of consciousness underwent radiological examinations that identified a 10-mm ruptured aneurysm in the anterior communicating artery. A microsurgery clip was performed to definitively treat the aneurysm and occurred without surgical complications. Molecular analysis of the material obtained revealed the presence of EBV DNA in the aneurysm wall. The patient died 21 days after admission due to clinical complications and brain swelling.

LESSONS This is the first description of the presence of herpesvirus DNA in a patient with IA, presented in 2.8% of our data. These findings highlight that viral infection may contribute to the pathophysiology and is an additional risk factor for IA formation, progression, and rupture by modulating vessel wall inflammation and structural changes in chronic infections.

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KEYWORDS intracranial aneurysm; intracranial hemorrhage; subarachnoid hemorrhage; human herpesvirus; HHV; inflammation

Subarachnoid hemorrhage (HSA) from a ruptured intracranial aneurysm (IA) is a leading cause of mortality worldwide among working-age patients. This clinical condition increases the risk of mortality by 50%, but the mechanisms leading to structural vessel wall weakening are unclear. Some risk factors are known, including female gender, age under 50 years, smoking, hyperlipidemia, aneurysm size ratio, polycystic kidney, multiple aneurysms, old cerebral infarct, family history, systemic arterial hypertension, Marfan and collagen syndromes, and Japanese and Finnish ethnicity.1,2 Nevertheless, currently risk factors do not explain why some people develop IA disease, have worse disease progression, or even rupture. Some questions persist, so the main hypothesis of this study is that the presence of the virus in the brain wall might lead to more inflammatory influence in the artery.

Human herpesviruses (HHVs) are the cause of several clinical conditions. Many diseases, such as rhinitis, encephalopathies, hepatitis, esophagitis, colitis, pneumonia, neonatal infections, febrile vesicles, genitai infections, vasculitis, ischemic attacks, thrombosis, atherosclerosis, cancer, neuroinflammatory diseases, giant cell arthritis, and granulomatous aortitis, have all been described as secondary to these viruses.5–6 Epstein–Barr virus (EBV), in particular, has been considered since 1990 to be an important pathogen in the pathophysiology of several
EBV, in its latent form, is present in more than 90% of the adult population, with saliva as the primary route of transmission, and is detected mainly in B lymphocytes and in the epithelium of oropharyngeal cells.

The recent worldwide concern about viral infection and neurological effects has led to the hypothesis of a relationship between chronic viral infection and cerebrovascular disease. The presence of chronic pathogens implies a local and systemic silent inflammatory response and plays a role in chronic vessel wall changes, leading to vasculitis and infestation viral in the brain wall. This report presents the first description of HHV deoxynucleotidylc acid (DNA) encountered in an IA and discusses the possible contribution of viral infection to the pathophysiology of IA formation and rupture.

**Illustrative Cases**

The study selected 401 patients from the São Paulo School of Medicine Clinics Hospital (HC-FMUSP) Department of Neurological Surgery. The patients were divided into 2 groups: ruptured aneurysm (244) and unruptured aneurysm (177). We excluded (366) IA. It was possible to collect surgically and analyze just (35) IA samples; these comprised (22) ruptured aneurysm and (13) nonruptured aneurysm.

The protocol started with obtaining biological material through vascular microsurgery procedures to remove aneurysm fragment samples performed at the surgical center of the Central Institute Department of Neurosurgery at HC-FMUSP. After collection, all samples were sent to the Virology Laboratory of the Instituto de Medicina Tropical of São Paulo in a freezer at −80°C. The human pan herpesviruses (HSV-1, HSV-2, EBV, cytomegalovirus [CMV], varicella zoster virus [VZV], HHV-6, HHV-7, and HHV-8) were selected and analyzed by polymerase chain reaction (PCR) targeting. These viruses were chosen because of high frequency, the presence of HHV deoxyribonucleic acid (DNA) encountered in an IA and discusses the possible contribution of viral infection to the pathophysiology of IA formation and rupture.

Molecular analysis was performed in order to verify the possible presence of 1 of the 8 types of herpesviruses in the patient’s aneurysmal wall. The procedure was conducted according to the technical specifications presented in Table 1. A positive PCR result was obtained for EBV (HHV-4), with a viral load of 12.163 copies/mL (Fig. 3).

**Discussion**

**Observations**

EBV infections have been linked to the occurrence of some brain and vascular diseases. For example, the EBV latent protein EBNA1 and the early lytic protein BZLF1 were found in astrocytes and microglia, in addition to B lymphocytes, in 82% of multiple sclerosis cases. The viral proteins were in an active state of transcription, indicating a possible correlation with the processes of inflammation and degeneration of neural tissue. A rare complication of EBV infection is encephalopathy, a
The condition caused by the immunotoxicity of EBV infection. This complication is generally restricted to children and immunocompromised patients, but it can affect immunocompetent adult patients. Case reports also indicate the occurrence of acute transverse myelitis and a combination of polyradiculitis and anterior horn syndrome in immunocompetent patients, as well as the possible development of neurological sequelae.

Chronic active EBV infections can show a wide variety of manifestations. The involvement of brain meninges, parenchyma, vascular system, epithelium, and lymphoid tissue has been reported as a cause of neurological disorders, such as dilation of spindle aneurysms, meningitis, meningoencephalitis, and disseminated encephalomyelitis. The vascular consequences on the central nervous system arise due to the direct invasion of the virus, the infiltration of lymphocytes infected by EBV, and the deposition of antigen-antibody complexes in the endothelium.

One of the major causes of morbidity in cardiovascular and cerebrovascular diseases is atherosclerosis. The etiopathogenesis of atherosclerotic plaques is similar to the chronic inflammatory process, and establishing an association with viral infections is possible. Studies have shown a high prevalence of EBV, as well as CMV and Torque Teno Virus (TTV), in atheroma plaques, supporting the hypothesis of viral etiology, especially in patients with vascular disorders.

High wall shear stress (WSS) can trigger proinflammatory signaling in endothelial cells (ECs), which then recruit macrophages through expression of chemoattractant protein 1 (MCP1). This process leads to the expression of proteases that are responsible for disruption of the vessel’s elastic lamina and for collagen remodeling, which includes changes in the orientation and type of fibers. These changes, in turn, lead to a focal outward bulging of the wall and the formation of intracranial aneurysms. In addition, high WSS leads to dysfunction and disruption of the ECs and generates an inflammatory process, which implies migration, changes in phenotype, and apoptosis of vascular smooth muscle cells through biochemical reactions.

Inflammation therefore determines the aneurysm formation and its progression to rupture. Consequently, modulating this process may be clinically significant. There are some studies that established CMV in abdominal aortic aneurysm, reinforcing the idea of virus influence in vascular wall response.
Chronic local inflammation might lead to artery systemic inflammation, weaken the arterial wall, and, consequently, form an AI, as well as assist with its rupture. This salient chronic infection can add to tradition risk factors (smoking, hypertension, and history family) and lead to aneurysm formation and rupture.

There are several limitations of this study. First, the interpretation of the results is limited by the small size of the sample, which is supported because of the technical difficulty to have eligible patient to have the sample collected in operating room. However, this is the first report to analyze HHV in a brain sample. More studies are needed to determine the exact relationship and establish cytokines and biomarkers involved in IA. Nevertheless, these findings may highlight a unique and important discussion regarding the understandable concern over the development of IA and rupture.

Lessons

This is the first description of the presence of herpesvirus DNA in a patient with IA, presented in 2.8% of our data. These findings highlight that viral infection may contribute to the pathophysiology and risk factors of IA formation, progression, and rupture by modulating vessel wall inflammation. More studies are needed to determine the exact relationship and to establish the cytokines and biomarkers involved in the viral IA infection.

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**Disclosures**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**Author Contributions**

Conception and design: Rabelo, Samaia da Silva Coelho, Tozetto Mendoza, Braz-Silva, Figueiredo. Acquisition of data: Rabelo, Telles, de Souza, Tozetto Mendoza, Braz-Silva, Figueiredo. Analysis and interpretation of data: Rabelo, Samaia da Silva Coelho, Telles, Tozetto Mendoza, Galvani de Oliveira, Braz-Silva, Figueiredo. Drafting the article: Rabelo, Samaia da Silva Coelho, Telles, Tozetto Mendoza, Galvani de Oliveira, Figueiredo. Critically revising the article: Rabelo, Samaia da Silva Coelho, Telles, Tozetto Mendoza, Galvani de Oliveira, Figueiredo. Reviewed submitted version of manuscript: Rabelo, Samaia da Silva Coelho, Coelho, Galvani de Oliveira, Braz-Silva, Teixeira, Figueiredo. Accepted the final version of the manuscript on behalf of all authors: Rabelo. Statistical analysis: Telles. Administrative/technical/material support: Coelho, Braz-Silva, Figueiredo. Study supervision: Coelho, Figueiredo.

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