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Case Report

Cerebral venous sinus thrombosis secondary to acute viral meningitis from cytomegalovirus and Epstein-Barr virus in immunocompetent patients: a case report

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ABSTRACT

Cerebral venous sinus thrombosis (CVST) represents about 0.5% to 3% of all stroke cases, with a higher prevalence among younger populations. The estimated incidence is around 3 to 4 cases per million in adults and 7 cases per million in children. In tropical areas, there is often a notable association between infectious diseases and strokes. In sub-Saharan Africa, infections are identified as significant risk factors for cerebral venous thrombosis. Human cytomegalovirus (CMV) and Epstein-Barr virus (EBV), both ubiquitous members of the herpesvirus family, are typically asymptomatic; however, they can, in certain instances, contribute to the development of thromboembolic diseases (TED), particularly in immunocompromised individuals. The incidence of CVST linked to CMV or EBV in immunocompetent individuals without other risk factors is uncommon. This study presents two cases: the first involves a 15-year-old immunocompetent adolescent who experienced a rapid decline in alertness, while the second case pertains to a 43-year-old man who presented with sudden-onset headaches. Magnetic resonance venography (MRV) revealed extensive CVST on the left side in the first case and a sub occlusion of the left transverse sinus in the second. Analysis of cerebrospinal fluid isolated EBV and CMV through PCR, with positive serological results. The clinical outcome was favorable due to anticoagulant treatment combined with symptomatic management of the infections. The risk of CVST should not be overlooked in patients with symptoms related to CMV and EBV infection regardless of immune status and MRV should be considered to rule out this possibility.

Keywords: Cerebral venous sinus thrombosis (CVST), Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Viral meningitis, Sub-Saharan Africa

INTRODUCTION

Infections are the leading risk factor for cerebral venous sinus thrombosis (CVST) in sub-Saharan Africa, contributing to a significantly higher mortality rate than that observed in developed nations.[1,2] Growing evidence suggests that viral infections can instigate thromboembolic diseases (TED), with the emergence of viruses like SARS-CoV-2 and its related thromboembolic complications provide additional support for this association.[3–7] Human cytomegalovirus (CMV), also known as human herpes virus 5 (HHV-5), along with Epstein-Barr virus (EBV), or human herpes virus 4, belong to the Herpesviridae family and are considered ubiquitous viruses.[8,9] In

immunocompetent adults, primary infections with CMV and EBV are symptomatic in less than 10% of cases, typically presenting as a mild mononucleosis-like syndrome.[9] Neurological manifestations are infrequent, primarily occurring as meningoencephalitis.[9] Conversely, in immunocompromised individuals, severe manifestations are common, particularly with a tropism for the central nervous system, affecting 5 to 10% of cases.[9] Although numerous instances of thromboembolic diseases associated with CMV and EBV have been reported in medical literature, often attributed to direct inflammatory mechanisms or antiphospholipid antibodies (APL).[5,10]

There are very few documented cases linking these infections specifically to cerebral venous thrombosis in immunocompetent patients without other prothrombotic risk factors.This study highlight two cases of cerebral venous thrombosis, the first involving a 15-year-old adolescent with lymphocytic meningitis associated with Epstein-Barr virus (EBV), and the second involving a 43-year-old adult with lymphocytic meningitis linked to cytomegalovirus (CMV). Both patients were immunocompetent and exhibited no thrombophilia abnormalities. This research represents the first of its kind in the sub-region.

CASE REPORTS

Case 1

A 15-year-old right-handed student has a medical history that includes hospitalization in our department approximately seven months ago for a cerebral venous thrombosis affecting the superior sagittal sinus, which was associated with aseptic meningitis. The patient exhibits sequelae including structural vascular epilepsy and left-sided hemiparesis, with a modified Rankin score of 1/5. The patient discontinued all medications, including anticoagulants and antiepileptic treatments, after two months of therapy due to financial difficulties, without consulting a neurologist.

Five days prior to his admission to our department, the patient exhibited a rapidly progressive disturbance of consciousness over a span of three days, accompanied by fever and myalgia. Initially treated at an urban hospital for severe malaria, there was no observed improvement in his condition. The deterioration of his alertness, coupled with focal onset tonic seizures (beginning in the right hemibody) that progressed to secondary generalization, necessitated the transfer of the child to our facility for more appropriate management. Upon admission, the neurological examination revealed a state of confusion (Glasgow Coma Scale score of 13/15), a non-massive right hemibody pyramidal syndrome, signs of infection, and meningeal syndrome.

The Magnetic resonance venography (MRV) revealed a venous thrombosis on the left side, affecting the transverse sinus, the sigmoid sinus, and the jugular vein (Figure 1). This was accompanied by venous infarcts exhibiting hemorrhagic transformation, with recent bilateral occurrences in the thalamus (Figure 2) and older lesions in the left superior frontal gyrus (Figure 3). The analysis of the cerebrospinal fluid (CSF) suggested lymphocytic meningitis, and polymerase chain reaction (PCR) testing confirmed the presence of Epstein - Barr virus (EBV) (Table 1). Serological tests for HIV, as well as hepatitis B and C, returned negative results. The autoimmune and thrombophilia workup returned negative results (Table 2). The patient was placed on anticoagulants, and concurrently, a corticosteroid treatment of 1 g of methylprednisolone was initiated for five days.

The patient's hospitalization was characterized by the development of a regressive tonic epileptic state under Levetiracetam at a dosage of 40 mg/kg. One week after admission, the patient experienced generalized dystonias, which were addressed with Trihexyphenidyl at a dosage of 2 mg three times daily, in conjunction with clobazam at 25 mg divided into three doses per day, resulting in a favourable clinical evolution. After a 40-day hospital stay, the patient was discharged in a conscious state, albeit with residual dystonic symptoms in the upper limbs. The patient continues to receive anticoagulant therapy, along with sodium valproate, baclofen, and clobazam. Follow-up consultations indicated the presence of bilateral hypoacusis as a sequela.

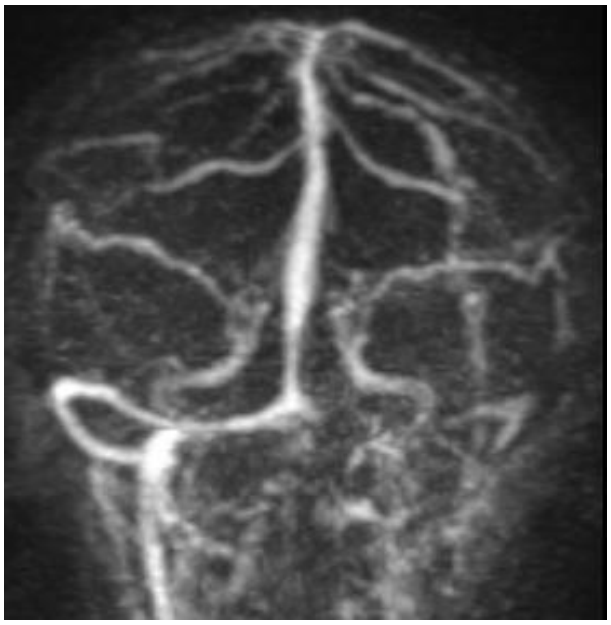

Figure 1: Brain MRV of Patient 1.

Case 2

A 44-year-old male police officer, who is right-handed and has a medical history of hypertension and dyslipidemia without ongoing treatment. Ten days prior to his admission to our facility, he experienced severe and diffuse headaches, rated 8 out of 10 on the visual analog scale (VAS), with pain radiating to the fronto-orbital region and

worsening at night. Accompanying these headaches were fever, myalgias, generalized body aches, and pronounced fatigue. This prompted a visit to an urban hospital, where he was initially treated for a suspected malaria episode; however, the headaches persisted, necessitating his transfer to our neurology department.

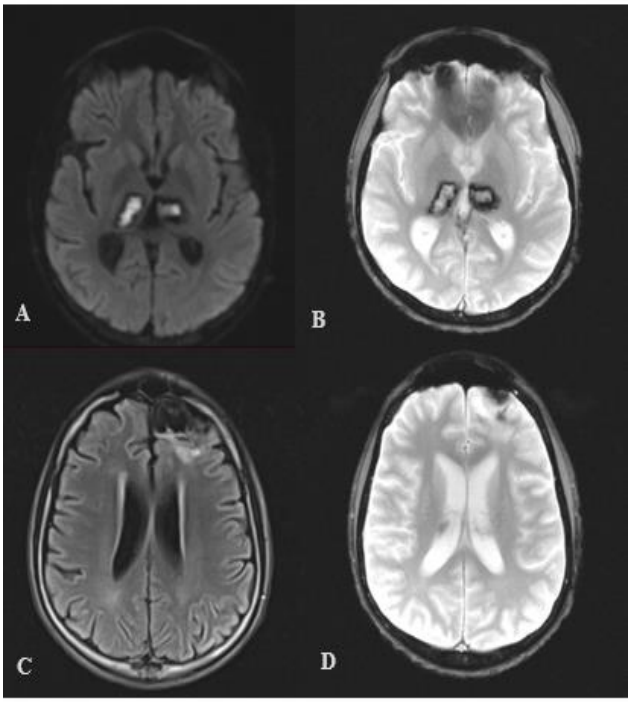

Figure 2 Brain MRI of patient 1. Hemorrhagic infarcts of varying ages are noted, including a semi-recent thalamic infarct that appears as a hyperintense signal on diffusion-weighted imaging (B1000) (A) and heterogeneous signal on T2*-weighted echo spin sequence (B). An older infarct in the left superior frontal gyrus is seen as a hypointense signal on fluid attenuated inversion recovery (FLAIR) imaging (C) and also shows heterogeneous signal on T2* imaging (D).

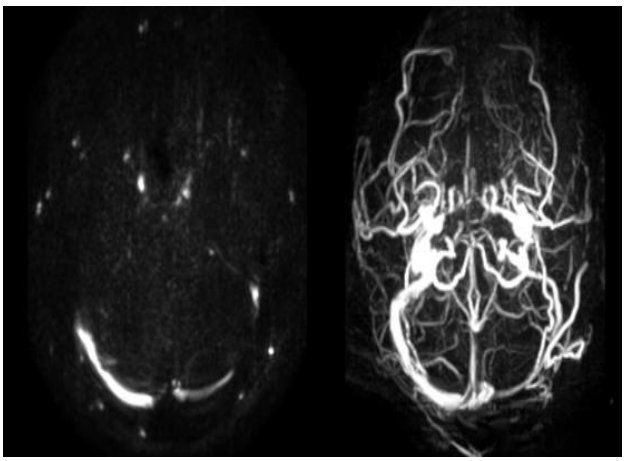

Figure 3: Brain MRV of patient 2. On the venography images, a sub occlusion of the left transverse sinus is observed.

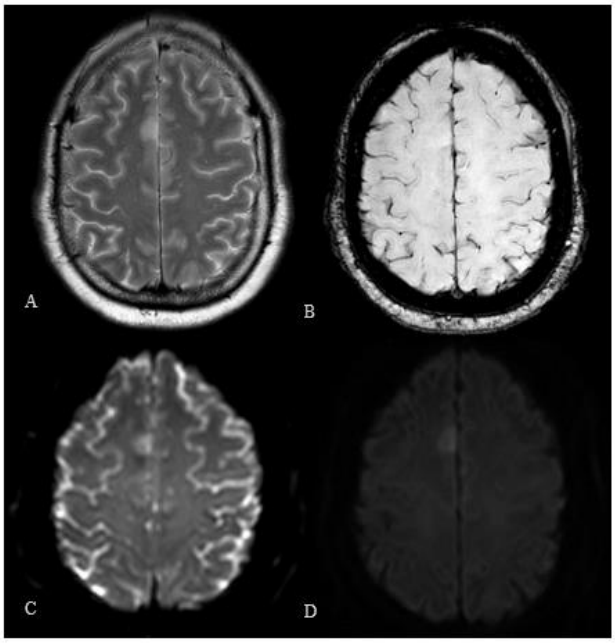

Figure 4: Brain MRI of patient 2. A venous infarction without hemorrhagic transformation is detected in the right semi-oval center, showing hyper intensity on T2 axial section (A). No signal abnormalities are present in T2* imaging (B), while hyper intensity appears in diffusion B1000 (D) without ADC restriction (C).

The initial neurological examination was unremarkable. However, a persistent evening-type fever was observed during the hospitalization. Brain MRI revealed a subocclusion of the left transverse sinus (Figure 4), leading to parenchymal effects manifested as a non-hemorrhagic venous infarct in the right oval center (Figure 5). Cultures from blood, urine, and CSF did not identify any pathogens. The analysis of the CSF suggested lymphocytic meningitis, and PCR testing confirmed the presence of cytomegalovirus (CMV) (Table 1). Serological tests for HIV, as well as hepatitis B and C, returned negative results. Additionally, assessments for autoimmune disorders and thrombophilia also yielded negative findings (Table 2). The patient's condition improved positively with anticoagulant therapy, which was continued for six months.

DISCUSSION

Stroke is a prevalent neurological disorder that is linked to high morbidity and mortality rates.[11] The 2019 Global Burden of Disease (GBD) Study estimated that there were over 12 million new cases of stroke worldwide. Stroke rank as the second leading cause of death globally, accounting for approximately 11.6% of all fatalities.[12] According to the World Health Organization (WHO), 85% of these deaths occur in low- and middle-income countries.11 CVST constitutes about 0.5% to 3% of all stroke types, primarily affecting younger individuals, with an estimated incidence of 3 to 4 cases per million in adults and 7 cases per million in children.[1,13] In Africa, there is a

significant link between infectious diseases and stroke, as infections can lead to strokes, including CVST, which presents with distinct clinical and radiological features, as well as specific prognostic and evolutionary patterns.[2,12] This study presents two cases of cerebral venous thrombosis associated with viral meningitis: one in a 43-year-old adult due to CMV and another in a 15-year-old adolescent due to EBV. Both patients responded well to anticoagulant therapy and conservative meningitis management.

Table 1: Analysis results of CSF.

Parameters	Patient 1	Patient 2	References values
Macroscopic analysis			
Appearance	Clear	Clear	Clear
Opening pressure	10 cm of water	12 cm of water.	from 10 to 15 cm of water
Cytology analysis			
WBC counts	13/mm^3	20/mm^3	<5/ mm^3
Red blood cell count	0/ mm^3	0/ mm^3	0/ mm^3
Atypical cells	0/ mm^3	0/ mm^3	0/ mm^3
Cytology formula			
Lymphocytes	100%	95%	Lymphocytes: 100%
Neutrophils	0%	5%	Neutrophils: 0%
Lymphoblasts	0%	0%	Lymphoblasts: 0%
Biochemical Analysis			
Proteinorrhachia	1.27 g/l	0.62 g/l	0.15 à 0.35 g/l
Glycorrhachia	0.79 g/l	0.67 g/l	0.45 à 0.80 g/l
Chlore	107 mmol/l	107 mmol/l	120 à 127 mmol/l)
Bacteriological analysis			
Cultures	No germ		No germ
Molecular biological analysis (PCR)			
MTB	Negative	Negative	Negative
Viruses	EBV positive	CMV positives	Negative
Immunological analysis			
TPHA	Negative	Negative	Negative
VDRL	Negative	Negative	Negative

WBC: White Blood Cells, Cm: Centimeter, PCR: polymerase chain reaction, MTB: Mycobacterium Tuberculosis, EBV: Epstein-Barr virus, CSF: Cerebrospinal Fluid, TPHA: Treponema Pallidum Hemagglutinations Assay VDRL: Venereal Disease Research Laboratory.

Table 2: Outcomes of autoimmunity and thrombophilia tests.

Tests and assay techniques	Patient 1	Patient 2	References values
ANA (IIF)	< 160	< 160	< 160
APL (ELISA)	1 U/ml	<1 U/ml	< 7 U/ml
ANCA (IIF)	< 20	< 20	< 20
Antithrombin (calorimetry)	-	109%	80-120%
C protein (calorimetry)	-	111%	70-140%
S protein (chronometry)	-	80%	59%
G20210G>A mutation (MCA)	-	Absent	Absent

ANA: Anti-nuclear antibodies, APL: Anti-phospholipid antibodies (the antibodies tested are anti-cardiolipin, anti-phosphatidylserine, anti-phosphatidylinositol, anti-phosphatidylethanolamine, anti-phosphatidic acid, and anti-beta 2-glycoprotein), ANCA: Anti-Neutrophil Cytoplasmic Antibodies, G20210G>A mutation: A Mutation in the Prothrombin Gene, IIF: Indirect Immunofluorescence, ELISA: Enzyme-Linked Immunosorbent Assay.

Hospital data from West Africa indicates that the prevalence of CVST ranges from 0.47% to 3%, with an acute mortality rate of approximately 10% in these regions.[2,14–16] CVST is a multifactorial condition; however, in nearly 80% of cases, a prothrombotic risk factor or a direct cause is identified.[17] In the context of sub-Saharan Africa, infections emerge as the leading risk factors for CVST, representing 63.1%, followed by the use of combined oral contraceptives (7.3%), pregnancy and postpartum conditions (6.2%), and coagulopathies (2.2%).[2] Shubhankar Mishra and colleagues noted that in children, infections and coagulopathies are the primary causes of CVST, occurring more frequently in males (60 to 70%), which contrasts with adult patterns.[18] Bacterial and viral infections are associated with an increased thromboembolic risk due to the systemic inflammation

they trigger.[6] Various viruses have been implicated in TED, including human immunodeficiency virus (HIV), herpes simplex virus (HSV), hepatitis C virus (HCV), varicella-zoster virus (VZV), H1N1 influenza virus, as well as cytomegalovirus (CMV) and Epstein-Barr virus (EBV).[6] The occurrence of TED linked to CMV is likely not infrequent, with a reported incidence of 6.4% in patients admitted for acute CMV infections.[10] The most common form of thrombosis is venous, typically presenting as deep vein thrombosis (DVT) in the lower extremities and pulmonary embolism, followed by splanchnic and portal vein thrombosis.[19]

In contrast, instances of CVST associated with CMV are rare, with the first documented case appearing in 1989 and a total of five cases recorded in the existing literature.[9,10,19–21] Although the risk is higher in immunocompromised patients, most cases occur in immunocompetent individuals.[7,19] CMV may induce thrombosis by infecting endothelial cells, leading to increased platelet adhesion, activation of factor X, elevated circulating factor VIII, and stimulation of anti-phospholipid antibody production.[7,10,19]

CMV is commonly recognized as a potential trigger for thrombosis in vulnerable individuals rather than a direct cause.[7] Additional factors, such as the use of combined oral contraceptives (COC), are present in up to 63% of patients, further contributing to the predisposition to thrombosis.[7] Among five documented cases, one patient was immunocompromised due to HIV, while four were immunocompetent. Of these, three had additional prothrombotic factors, including COC use in two cases and a factor V Leiden mutation plus COC use in one patient.[19–21]

The case reported by Shany et al. was previously the only one to document a thrombosis associated with CMV without any other prothrombotic factors, involving a 70-year-old man.[10] Our study represents the second such case, with thrombophilia assessments yielding negative results, as did antiphospholipid antibody tests and autoimmune evaluations.

The prognosis is generally favourable and is contingent upon the prompt initiation of treatment, as early diagnosis and management of CVST could potentially decrease the mortality rate to between 5% and 15%.[22] Antiviral etiological treatment is typically advised only for immunocompromised patients and aligns with the standard treatment protocols for CVST. In this context, anticoagulant therapy was administered for a duration of six months, resulting in a positive clinical outcome.

Although cases of TED associated with CMV have been frequently documented in the medical literature, there is a notable scarcity of references to TED associated with EBV, with most cases occurring in immunocompromised individuals.5 To date, there is only one known case of CVST associated with EBV in an immunocompetent individual.[23] The mechanisms by which EBV infection may lead to thrombosis remain partially unclear. Potential factors could include temporary increases in anti-phospholipid antibodies and oxidative damage to endothelial cells induced by EBV.[5,23] Most reported cases tested positive for anti-phospholipid antibodies; however, our patient was immunocompetent with negative results for these antibodies. The patient underwent anticoagulant therapy for six months, in addition to a five-day corticosteroid treatment. The child experienced residual hypoacusis, which cannot be directly attributed to EBV, considering the significant vascular and parenchymal complications.

A comprehensive understanding of the direct role of the virus in the development of CVST through large-scale studies could enhance the formulation of preventive and therapeutic strategies for patients at an increased risk of thrombosis associated with EBV and cytomegalovirus CMV infections.

CONCLUSION

CVST is a multifactorial condition where infections, especially in tropical areas, significantly contribute to its development. The risk of CVST should not be overlooked in patients with symptoms related to CMV and EBV. Clinicians must recognize this association, particularly in patients with sudden or rapidly worsening neurological symptoms and fever, regardless of immune status, especially in individuals with HIV, those with neoplasia, or post-transplantation. Magnetic resonance venography should be considered to rule out this possibility. Furthermore, the initiation of anticoagulant therapy should not be delayed to optimize the prognosis, while specific antiviral treatment is reserved for immunocompromised patients

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