Title: Hypercoagulability and Cavernous Sinus Thrombosis due to Protein C Deficiency. A Case Report

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Author names: Wilson S. Peñafiel-Pallares[1], Camila Brito-Balanzátegui[1], Jaime David Acosta-España[2,3,4*].

Degrees and Affiliations:

[1]Fifth-year Medical Student. School of Medicine, Universidad de las Américas, Quito, Ecuador.

[2]Medical Doctor, Reasercher, Ph.D. student. Institute of Microbiology, Friedrich Schiller University Jena, Jena, Germany.

[3]Senior Lecturer. Postgraduate Program in Infectious Diseases, School of Medicine, Pontificia Universidad Católica del Ecuador, Quito, Ecuador.

[4]Researcher. Centro de Investigación para la Salud en América Latina (CISeAL), Pontificia Universidad Católica del Ecuador, Quito, Ecuador

ORCID (Open Researcher and Contributor Identifier):

https://orcid.org/0000-0002-9896-6991

https://orcid.org/0000-0001-8543-5406

https://orcid.org/0000-0001-5299-2732

About the author: WSP is a fifth-year (5/6) medical student from Quito-Ecuador. He is interested in anesthesiology, pediatrics, and internal medicine. His focus is on clinical practice and research. He has experience in public and private health centers in the country and abroad. His volunteer work is broad and focuses mainly on providing health services to the neediest communities in South America.

Corresponding author email: jdae_14@hotmail.com

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Highlights

- Patients with undiagnosed thrombophilia have a risk of 3-8% of developing cerebral venous thrombosis.
- 3-4 per million cases may develop cerebral venous thrombosis, which can be later complicated by a septic cavernous sinus thrombosis.
- Patients complicated with septic cavernous sinus thrombosis demonstrated to have sphenoidal rhinosinusitis in 57% of the cases.
- A middle-aged patient without any medical or family history of thrombophilia, can develop a cerebral venous thrombosis due to Protein C Deficiency.

- A combination of a septic cavernous sinus thrombosis and a thrombophilia can be correctly managed with early anticoagulation and antibiotic treatment.

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- #Hypercoagulability
- #ProteinCDeficiency
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ABSTRACT.

Introduction: Thrombophilia due to protein C deficiency is an unusual condition, present in 0.2% of general population. Cerebral venous thrombosis has an incidence of 3-4 cases per million in adults. A combination of both is very uncommon. Patients with these conditions are prone to acquiring life-threatening superinfections. **Case:** A 51-year-old woman presented with pressing frontal headache accompanied by left periorbital edema, fever, diplopia, and disorientation. Laboratory findings showed low protein C levels. Computed tomography demonstrated sphenoidal rhinosinusitis. Magnetic Resonance Venography revealed cavernous sinus thrombosis. The patient was treated with empiric antibiotic treatment (vancomycin, ceftriaxone, and metronidazole) and anticoagulants. **Conclusion:** This case report emphasizes the importance of early diagnosis and appropriate management of patients with protein C deficiency complicated by septic cavernous sinus thrombosis.

Key Words: Thrombophilia; Protein C deficiency; Cavernous sinus thrombosis; Case report

INTRODUCTION.

Protein C deficiency (PCD) is a rare disorder with a prevalence of approximately 0.2% in general population.[1,2] Protein C is a vitamin K-dependent glycoprotein activated by the thrombin-thrombomodulin complex on the endothelial surface. The activated Protein C degrades factors Va and VIIIa, thereby, inhibiting coagulation. It is also involved in regulating the expression of the endothelial cells genes of proteins related to inflammation and cell survival.[3] PCD promotes thrombus formation. In particular, it can occur as an autosomal dominant inherited disease with an alteration of the Protein C Inactivator of Coagulation (PROC) gene or, less commonly, as an acquired disease.[4] It may be decreased in right heart failure, severe liver disease, acute inflammation, and respiratory syndromes by consumption and dysfunctional production of activated Protein C.[2] There are two phenotypes of PCD: type 1, is described as a mutation that reduces the plasmatic concentration of Protein C antigen and its activity. Whereas, type 2, is characterized by normal concentrations of the protein, but dysfunctional activity.[2] This deficiency has a wide range of manifestations, from asymptomatic to life-threatening conditions.[4]

Cavernous sinus thrombosis (CST) belongs to the group of cerebral venous thrombosis. It has nonspecific clinical manifestations such as headache, painful ophthalmoplegia, conjunctival chemosis, and ocular proptosis.[5,6] CST can be either septic or aseptic. Septic form is the most common. The most reported causative microorganism is methicillin-resistant *Staphylococcus aureus* (MRSA), followed by Methicillin sensitive *Staphylococcus aureus* (MSSA).[7,8] In a literature review it was found that 57% of patients with septic CST, had sphenoidal rhinosinusitis (inflammation of the nasal mucosa (rhinitis) and of the mucosa of the paranasal sinuses (sinusitis)).[8]

THE CASE

A 51-year-old female patient with unremarkable medical history (non-previous similar events, nonsmoker, no surgeries, no miscarriages, non-contraceptive pills use) and without family history of thrombophilia, presented to the emergency department with a bilateral pressing frontal headache that had been present for 3 months, increased gradually in severity, and did not respond to acetaminophen. A non-contrast computed tomography showed sphenoidal rhinosinusitis, A parenchymal lesion was excluded. The patient was diagnosed with migraine and NSAIDs were prescribed. Non-treatment for rhinosinusitis was indicated. After 2 weeks, headaches worsened, and her family needed to take her back to the emergency department. During this admission, the patient had left periorbital edema, diplopia, and disorientation in time and place. Physical examination revealed left eye proptosis, nystagmus, limitation of extraocular movements, and papilledema with tortuous left retinal veins on fundoscopy. Remarkable vital signs were Respiration rate of 22/min, Temperature of 38.1°C and Pulse rate of 110/min.

Procalcitonin levels were 0.783 ng/ml (<0.5 ng/ml normal ranges). Neutrophils levels 14107 mm^3 (2000-8000mm^3 normal ranges). C-Reactive Protein levels 235.9mg/L (0-10mg/L normal ranges). D-Dimer 819 mg/ml (0-500 normal ranges). Prothrombin time, INR and Partial Thromboplastin Time were within normal ranges. Lipid panel, liver and renal function markers were normal. Antinuclear antibodies and anti-dsDNA were negative. Because of the possibility of periorbital cellulitis and infection, intravenous empiric antibiotic treatment was started with vancomycin (loading dose: 15mg/kg/ BID), ceftriaxone (2g/BID) and metronidazole (500mg/ TID). Urine and blood cultures were taken before antibiotic treatment, and both were negative. Based on the neurological findings, imaging studies of the brain were indicated. Magnetic Resonance Venography showed filling defects of the left cavernous sinus compatible with cavernous sinus thrombosis. Because of radiological findings, anticoagulation was started with enoxaparin (1mg/kg BID, total dose 60mg BID). Hemorrhage and infections of the central nervous system were excluded based on clinical presentation, laboratory and imaging studies.

Hypercoagulability tests revealed reduced functional and antigenic plasmatic Protein C levels (type 1 protein C deficiency) of 30.98% (70%-140% normal ranges). Antiphospholipid antibodies, protein S, antithrombin III, and homocysteine levels were within normal ranges. Factor V Leyden and prothrombin mutations were not detected. After seven days of hospitalization, laboratory findings were consistent with resolution of the infectious process (procalcitonin of 0.208 ng/ml, C-Reactive Protein of 40.10mg/L and neutrophils of 5239mm^3). Blood and urine cultures remained negative. The patient showed significant clinical improvement and was discharged on oral antibiotics (amoxicillin/clavulanic acid 1g/ BID for 5 weeks) and long-term oral anticoagulants (Dabigatran 150mg/ BID). Follow-up by hematology was indicated after 6 months of discharged and then, every year. At 8 months, imaging studies were consistent with complete resolution of the thrombotic event and sphenoidal rhinosinusitis.

DISCUSSION.

This case report presents a patient with thrombophilia due to type 1 PCD complicated by cavernous thrombosis. Septic CST was supported by periorbital cellulitis and laboratory findings. Weerasinghe & Lueck *et al*. reported a similar case with septic CST caused by MSSA, but their patient did not have 3 months headaches history, diplopia or fundoscopic abnormalities.[8] Type 1 PCD was suspected due to low Protein C plasmatic levels associated with a thrombotic event. In contrast to a case described by Fukushima *et al.* were normal plasmatic Protein C levels with dysfunctional activity, confirmed a type 2 PCD. Their patient manifested with seizures and paralysis. [9] The diagnosis in our patient was obtained by Protein C activity assay by immunofluorescence method, but genetic analysis was preferred in Fukushima´s *et al* report. [9] The risk of venous thromboembolism in patients with PCD, is around 3-8%.[1]

Cavernous thrombosis as a complication of an infectious process, is more common in patients who have prothrombotic risk factors such as: deficiency of coagulation factors, trauma, smoking, oral contraceptive pills use or surgeries.[2,5] (Figure 2). The aforementioned risk factors were not mentioned by the patient during the clinical interview. This supports the hypothesis of a possible inherited PCD triggered by an unidentified infection.[4] There have been some case reports of patients without any family history of hypercoagulable states that developed a thrombotic event and found to have thrombophilia.[2]

The imaging studies recommended for the diagnosis of CST are contrast-enhanced computed tomography, magnetic resonance imaging, or magnetic resonance venography. [7] In this patient, all these methods were used. Magnetic Resonance Imaging was normal, and contrast enhanced computed tomography revealed sphenoidal rhinosinusitis. Magnetic Resonance Venography showed enlargement and filling defect in the left cavernous sinus after contrast administration. Tortuosity and dilatation of the left ophthalmic veins were present. Central filling defects in the left transverse and sigmoid sinuses accompany these findings (Figure 1).

Because of uncertain course of time of sphenoidal rhinosinusitis, recommended 10 days antibiotic treatment was extended to 5 weeks. According to the management of chronic rhinosinusitis described by Baron & Durand in 2017, they recommend a minimum of 3 weeks of antibiotic course. Some symptoms of chronic rhinosinusitis tend to reappear 2-3 days after 10 days of treatment.[10]

At 8 months, imaging studies were consistent with complete resolution of the thrombotic event and sphenoidal rhinosinusitis. The continuation of anticoagulation with a direct oral anticoagulant (Dabigatran) after hospitalization, showed no recurrence of thrombotic events, similarly to Fukushima *et al*. [9]

The limitations of this case were the uncertainty about infectious etiology due to negative cultures. Also, a nasopharyngeal swab for bacteria was not performed. Due to a possible chronic sphenoidal rhinosinusitis as the infectious source, empirical prolonged antibiotic treatment was prescribed (this is debatable). Moreover, because of diplopia, confrontation visual field examination could not be assessed correctly.

CONCLUSIONS.

Although rare, a patient without medical and family history of thrombophilia, may develop cerebral venous thrombosis as a result of Protein C Deficiency. Sinus infection may worsen the clinical state. Early recognition with clinical examination and imaging studies followed by prompt intervention with anticoagulation and broad-spectrum antibiotics, is associated with a good prognosis for patients with septic CST due to hypercoagulability

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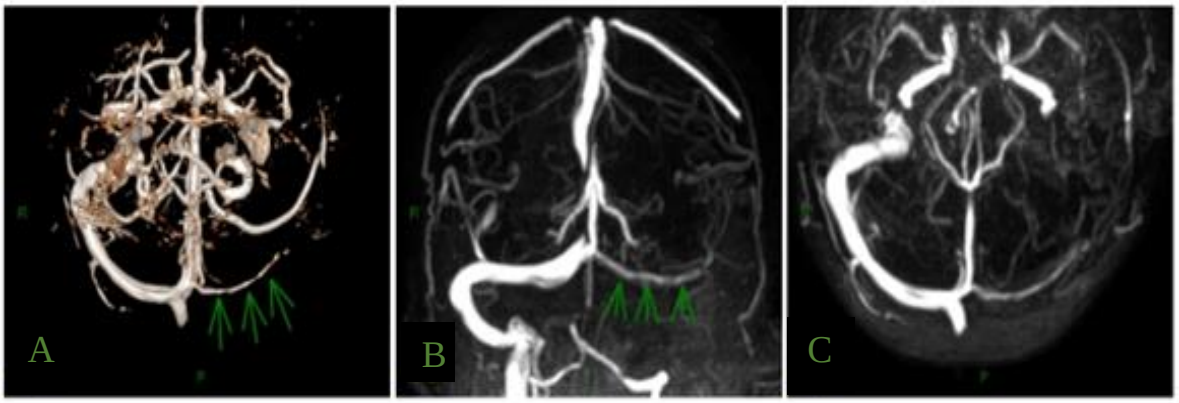
SUMMARY - ACCELERATING TRANSLATION

Este reporte de caso presenta a un paciente con trombofilia debido a una deficiencia de proteina C (DPC) tipo 1 complicado por una trombosis del seno cavernoso (TSC). La TSC séptica fue confirmada por celulitis periorbitaria y hallazgos de laboratorio. El paciente también presentaba historia de dolores de cabeza de 3 meses, diplopía y anormalidades fundoscópicas. La sospecha de DCP tipo 1 surgió debido a bajos niveles plasmáticos de Proteína C asociados con un evento trombótico. La tomografía computarizada mejorada con contraste y la resonancia magnética venográfica mostraron un aumento y un defecto de llenado en el seno cavernoso izquierdo después de la administración de contraste, así como tortuosidad y dilatación de las venas oftálmicas izquierdas. Se recomendó un tratamiento prolongado de 5 semanas con antibióticos debido a una posible rinosinusitis esfenoidal crónica como fuente infecciosa. En el seguimiento a los 8 meses, se observó una resolución completa del evento trombótico y de la rinosinusitis esfenoidal. Se realizó anticoagulación oral (Dabigatrán) después del alta hospitalaria, lo que evitó la recurrencia de eventos trombóticos. Las limitaciones del caso incluyen la falta de cultivos positivos y la ausencia de una muestra de hisopado nasofaríngeo para bacterias.

1 **FIGURES AND TABLES.**

Figure 1. Brain Magnetic Resonance Venography Confirming Cavernous Sinus Thrombosis.



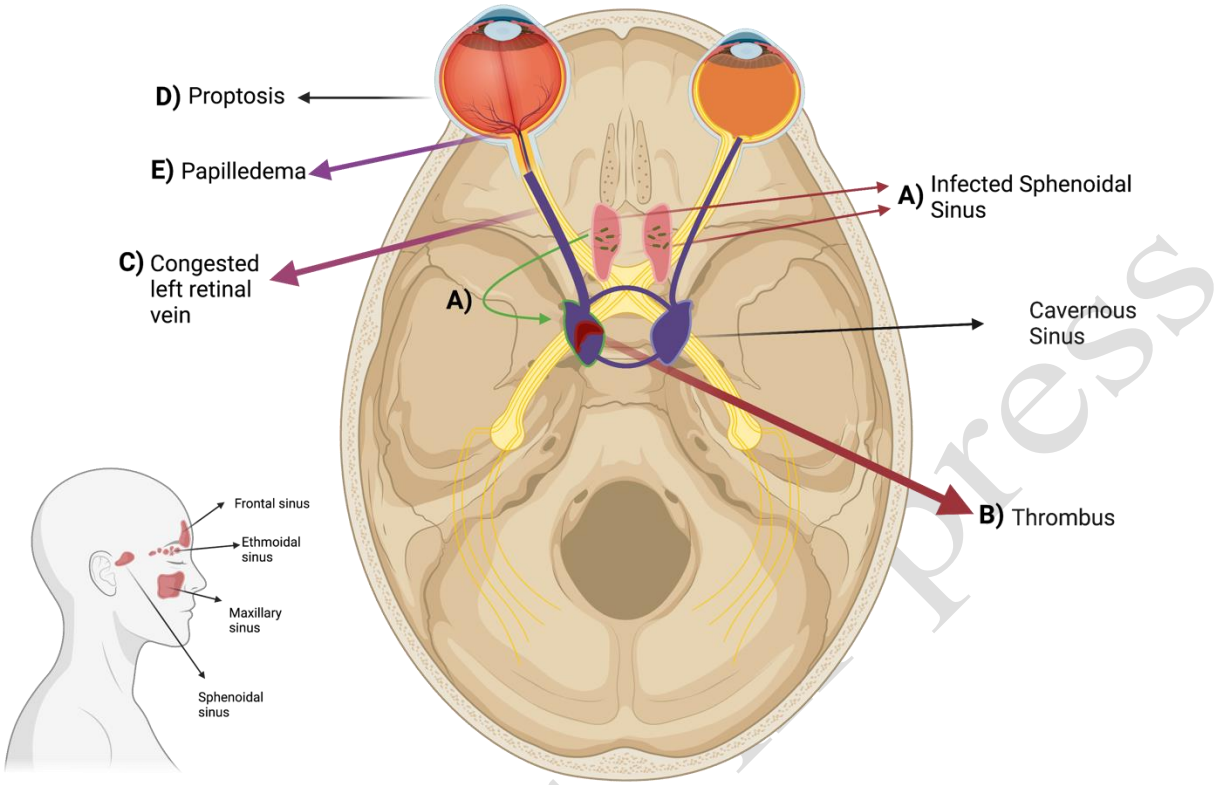
Legend: A: 3D *Reconstruction of a Magnetic resonance cerebral venography. Axial section, cranial view.* ***B:*** *Magnetic resonance cerebral venography. Coronal section.* ***C:*** *Magnetic resonance cerebral venography. Axial section, cranial view. All of them show d*ecreased diameter, signal intensity and filling defects of the left transverse sinus and ipsilateral internal jugular vein (green arrows). Tortuosity and dilatation of the left ophthalmic veins are also present.

2

3

1

Figure 2. Simplified Graphic of an Infected Cavernous Sinus Thrombosis



A) An infected sphenoid sinus causes septic thrombosis in the cavernous sinus, B) In cavernous thrombosis, the facial vein, and superior and inferior ophthalmic veins (C) cannot drain properly, resulting in facial and periorbital edema, ptosis, proptosis (D), chemosis, eye movement discomfort, papilledema (E), retinal vein dilation, and vision loss. This image was created with Biorender.

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