



Synergistic Impact of Dual Hereditary Protein C and S Deficiency Exacerbated by Acute Pan-Sinusitis in Recurrent Cerebral Venous Sinus Thrombosis: A Case Report

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ABSTRACT

Cerebral venous sinus thrombosis is a rare neurovascular emergency characterized by thrombotic occlusion of the dural venous sinuses. While various prothrombotic states predispose individuals to this condition, the concurrent presentation of dual hereditary Protein C and Protein S deficiency is exceptionally uncommon. This dual coagulopathy severely impairs natural anticoagulant mechanisms. We report the case of a 49-year-old male presenting with severe postural dizziness, vertigo, and bilateral lower extremity paresthesia. The patient had a history of a previous cerebral venous sinus thrombosis diagnosed in September 2023, for which he was receiving warfarin. Due to historically variable international normalized ratio levels and new symptoms, a comprehensive re-evaluation was initiated. Neuroimaging confirmed acute extension of the thrombosis involving the superior sagittal, left transverse, and left sigmoid sinuses, alongside an incidental finding of acute pan-sinusitis. To eliminate the confounding effect of warfarin on thrombophilia screening, the patient was bridged to low-molecular-weight heparin for fourteen days prior to testing. Subsequent functional assays confirmed profound deficiencies in Protein C (26 IU/dL) and Protein S (13 IU/dL). Management involved treating the regional pan-sinusitis and a strategic pharmacological transition to rivaroxaban (20 mg daily), resulting in complete clinical stabilization. In conclusion, this case underscores the necessity of rigorous methodological timing in thrombophilia testing and highlights regional inflammation as a potent acute trigger in genetically susceptible individuals. It further demonstrates the long-term viability of direct oral anticoagulants in complex dual inherited coagulopathies.

1. Introduction

Cerebral venous sinus thrombosis represents a relatively rare but potentially catastrophic cerebrovascular disorder, historically accounting for a small fraction of all acute stroke presentations globally. Unlike typical arterial ischemic strokes, which predominantly afflict older populations burdened with chronic atherosclerotic risk factors, cerebral venous sinus thrombosis possesses a unique

demographic and epidemiological profile. It frequently targets younger adults, particularly women of childbearing age, and presents with a highly variable and often deceptive clinical spectrum ranging from isolated, progressive headaches to severe encephalopathy, focal neurological deficits, symptomatic epilepsy, and profound coma.¹

Historically, the global incidence of this neurovascular emergency was estimated at



approximately three to four cases per one million individuals annually.² However, recent epidemiological shifts observed across international tertiary care centers suggest a rapidly rising diagnostic incidence. This perceived increase does not necessarily reflect a true rise in disease occurrence but is rather likely attributable to the widespread accessibility and dramatic advancements in non-invasive neuroimaging modalities. The shift away from invasive traditional cerebral angiography toward highly sensitive magnetic resonance imaging and magnetic resonance venography has allowed clinicians to detect partial thromboses and less severe cases that would have previously remained undiagnosed or misattributed to benign intracranial hypertension.

To comprehend the clinical severity of cerebral venous sinus thrombosis, one must first analyze the unique anatomical and physiological properties of the intracranial venous drainage system. The dural venous sinuses are rigid, endothelium-lined channels formed between the periosteal and meningeal layers of the dura mater. Unlike peripheral veins, these structures are completely devoid of valves, allowing for bidirectional blood flow dictated purely by pressure gradients.

The pathogenesis of thrombotic occlusion within this specialized environment is intrinsically multifactorial and is most accurately conceptualized through the classic framework of Virchow's triad: endothelial injury, venous stasis, and systemic hypercoagulability.³ Venous stasis in the cerebral sinuses can occur due to anatomical variations, low-flow states, or extrinsic compression. Endothelial injury may arise from mechanical trauma, invasive neurosurgical procedures, or contiguous regional infections. However, among the diverse etiologies driving the initiation and propagation of the dural thrombus, the hypercoagulable state is arguably the most critical and complex. While hypercoagulability can be acquired through conditions such as pregnancy, malignancy, or severe systemic infections,

inherited thrombophilias play a profoundly pivotal role, predisposing otherwise healthy individuals to spontaneous and recurrent neurovascular events.

Within the intricate equilibrium of the human coagulation cascade, the prevention of unchecked thrombosis relies heavily on a highly specialized regulatory feedback loop known as the natural anticoagulant pathway. Protein C and Protein S serve as the central, synergistic components of this vital physiological system. Both are vitamin K-dependent glycoproteins synthesized primarily in the liver, meaning their functional maturation requires a specific post-translational modification known as gamma-carboxylation, a process dependent on the vitamin K epoxide reductase enzyme.⁴

The activation of this regulatory pathway is a masterpiece of biological feedback. When the coagulation cascade is triggered and thrombin is generated to form a clot, excess thrombin escapes the immediate site of injury and binds to thrombomodulin, an integral membrane protein expressed on the surface of intact, healthy vascular endothelium.⁵ This thrombin-thrombomodulin complex undergoes a profound conformational shift, altering thrombin's substrate specificity from procoagulant to anticoagulant. This complex then rapidly cleaves circulating zymogen Protein C into its active enzymatic form, Activated Protein C.

However, Activated Protein C cannot function efficiently in isolation. To achieve its full proteolytic potential, it must bind to its essential, non-enzymatic cofactor, free Protein S, on the phospholipid surface of the cell membrane. Once formed, this highly efficient Activated Protein C-Protein S complex exerts profound anticoagulant effects by targeting the amplification phase of the coagulation cascade. It specifically and irreversibly proteolyzes and inactivates two critical procoagulant cofactors: Factor Va and Factor VIIIa. By dismantling these cofactors, the complex essentially neutralizes the prothrombinase and tenase complexes, thereby rapidly shutting down further massive



thrombin generation and halting the propagation of the thrombus.⁶

While isolated hereditary deficiencies of either Protein C or Protein S are well-documented and recognized independent risk factors for deep vein thrombosis and pulmonary embolism, the concurrent hereditary deficiency of both proteins represents an exceptionally rare and dangerous genetic anomaly. When a patient harbors a dual hereditary deficiency, the physiological consequences are not merely additive; they are severely synergistic. In this dual-defect scenario, the patient lacks both the primary active enzyme (Protein C) and the requisite spatial cofactor (Protein S) necessary to maintain hemostatic balance. This results in a catastrophic failure of the regulatory feedback loop. Without the ability to degrade Factor Va and Factor VIIIa, the coagulation cascade remains perpetually primed in the amplification phase. The consequence is massive, unregulated, and sustained thrombin generation upon the slightest physiological provocation. This exponential magnification of thrombotic risk predisposes these individuals to unusual, severe, and recurrent thrombotic events, frequently involving atypical anatomical locations such as the cerebral dural venous sinuses or the splanchnic circulation.⁷

Identifying a dual inherited deficiency presents significant methodological challenges in clinical practice. Accurate laboratory diagnosis requires highly specific functional assays. However, the timing of these diagnostic tests is fraught with confounding variables that can easily lead to misdiagnosis. Testing during an acute thrombotic event is highly problematic because natural anticoagulants like Protein C and Protein S are actively consumed in the process of attempting to regulate the massive clot formation, leading to transiently low serum levels that mimic a genetic deficiency.⁸ Furthermore, the administration of specific anticoagulant therapies drastically alters the biochemical landscape. Because Protein C and Protein S are vitamin K-dependent, the

initiation of vitamin K antagonists profoundly suppresses their hepatic synthesis. If a patient's blood is drawn for thrombophilia screening while they are actively taking a vitamin K antagonist, the functional assays will inevitably return critically low levels, yielding a false positive for an inherited deficiency. Thus, establishing a true genetic diagnosis requires rigid adherence to a strict chronological methodology, typically involving a deliberate transition to an alternative, non-vitamin K-dependent anticoagulant bridge to allow the intrinsic protein levels to normalize prior to serum analysis.

Historically, the absolute cornerstone of long-term therapeutic anticoagulation for cerebral venous sinus thrombosis, particularly cases occurring secondary to severe inherited thrombophilias, has been the utilization of vitamin K antagonists such as warfarin.⁹ Warfarin achieves anticoagulation by inhibiting the vitamin K epoxide reductase complex, thereby depleting the functional reserves of procoagulant factors II, VII, IX, and X. Despite its historical efficacy, warfarin therapy is burdened by significant clinical limitations. It possesses an exceptionally narrow therapeutic index, requiring constant vigilance and frequent phlebotomy to monitor the international normalized ratio. Furthermore, its pharmacokinetics are notoriously erratic, highly susceptible to dietary fluctuations in vitamin K intake, genetic variations in liver metabolism, and extensive drug-drug interactions. For patients with a high baseline hypercoagulability, subtherapeutic drops in the international normalized ratio can rapidly result in recurrent, life-threatening cerebral thromboses.

Consequently, the management paradigm for complex neurovascular and hematological disorders is currently undergoing a significant and necessary transition toward direct oral anticoagulants, also known as non-vitamin K antagonist oral anticoagulants. Agents such as rivaroxaban function through a distinctly different mechanism: the direct, competitive, and reversible inhibition of active Factor



Xa. Factor Xa represents the critical convergence point of both the intrinsic and extrinsic coagulation pathways. By directly targeting Factor Xa, these newer agents effectively bypass the upstream regulatory defects present in Protein C and Protein S deficiency. They directly arrest the thrombin burst without relying on the patient's compromised natural anticoagulant pathway. This targeted pharmacological approach, combined with highly predictable pharmacodynamics, the elimination of routine laboratory monitoring, and a standardized dosing regimen, offers a profound improvement in therapeutic reliability and patient quality of life.

Beyond systemic genetic vulnerabilities, the initiation of a cerebral venous clot often requires an acute precipitating event, acting as a secondary trigger. The anatomical continuity of the human skull provides a unique pathway for localized pathology to influence central neurovascular structures. The paranasal sinuses, comprising the maxillary, frontal, ethmoidal, and sphenoidal cavities, share a direct and complex venous drainage network with the intracranial dural venous sinuses via a system of valveless emissary veins.

Because these veins lack one-way valves, increased pressure or severe local inflammation within the facial and paranasal structures can facilitate the retrograde transmission of localized inflammatory mediators directly into the cerebral venous circulation. Acute regional infections, such as severe pan-sinusitis, provoke a potent localized immune response characterized by the dense release of pro-inflammatory cytokines. These cytokines severely disrupt the local dural venous endothelium, downregulating its natural antithrombotic properties and upregulating the expression of tissue factor. When this localized inflammatory endothelial injury occurs in a patient already harboring a profound systemic hypercoagulable state due to dual hereditary thrombophilia, the threshold for massive thrombosis is easily breached, leading to rapid, symptomatic clot

propagation.¹⁰

The primary aim of this report is to elucidate the complex pathophysiological interplay in a patient with a dual hereditary deficiency of Protein C and S presenting with recurrent cerebral venous sinus thrombosis. The novelty of this study lies in addressing the strict methodological requirements for accurate thrombophilia testing, documenting the successful clinical transition from variable vitamin K antagonist therapy to rivaroxaban, and exploring the underreported role of adjacent regional inflammation as an acute prothrombotic trigger.

2. Case Presentation

Ethical considerations and consent

Prior to the initiation of data collection and manuscript preparation, strict adherence to institutional and international ethical standards was ensured. This clinical case report was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained directly from the patient for the publication of this medical case, including all accompanying anonymized clinical data, laboratory results, and radiological imaging. Institutional Review Board exemption was granted by the local ethics committee at Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Indonesia, as this manuscript constitutes a retrospective observational report of a single patient with completely de-identified data, involving no experimental interventions outside the standard of care.

Patient demographics and initial clinical presentation

A 49-year-old male of Indonesian descent presented to the outpatient neurovascular clinic in May 2024 with a primary, debilitating complaint of episodic, severe postural dizziness and true room-spinning vertigo. The patient described the vertiginous episodes as a profound sensation of impending falls



and severe spatial disorientation, which was critically exacerbated by positional changes, specifically when transitioning rapidly from a supine or seated position to an upright stance. This vestibular instability severely restricted his daily ambulation and occupational functions. Concurrently, the patient reported the insidious onset of symmetrical, bilateral paresthesia affecting both lower extremities. He characterized this sensory disturbance as a continuous pins-and-needles sensation distributed primarily across the L4 through S1 dermatomes, persisting unabated for approximately four weeks prior to the current clinical evaluation. Upon detailed systemic inquiry, the patient emphatically denied any recent onset of focal unilateral motor weakness, facial

asymmetry, dysarthria, dysphagia, visual field deficits, or unprovoked, unintentional weight loss.

A comprehensive review of the patient's longitudinal medical records revealed a highly significant and complex neurovascular history (Table 1). The patient had sustained an initial, confirmed diagnosis of cerebral venous sinus thrombosis in September 2023, which had precipitated an associated ischemic stroke localized to the cerebral cortex. Following this acute event, he developed symptomatic secondary epilepsy, characterized by focal seizures with secondary generalization. The most recent clinically documented seizure occurred contemporaneously with the initial stroke presentation in September 2023.

Table 1. Chronological Timeline of Clinical Events

Date	Clinical Event / Intervention	Rationale / Outcome
September 2023	Initial presentation with ischemic stroke and diagnosis of cerebral venous sinus thrombosis. Initiated on a vitamin K antagonist (warfarin).	Targeted early anticoagulation to halt initial thrombus propagation.
Oct 2023 - April 2024	Outpatient monitoring of clinical status and coagulation profile.	Highly labile international normalized ratio (INR) fluctuations noted, ranging from 1.2 to 3.8 despite reported medication compliance.
May 2024	Onset of severe postural dizziness, true room-spinning vertigo, and bilateral lower extremity paresthesia.	Prompted urgent clinical re-evaluation due to suspicion of recurrent neurovascular compromise.
June 12, 2024	Advanced neuroimaging performed, utilizing Magnetic Resonance Venography and a dedicated paranasal CT-scan.	Confirmed acute thrombus extension into the superior sagittal, transverse, and sigmoid sinuses, alongside an incidental finding of acute purulent pan-sinusitis.
June 15, 2024	Inpatient admission. Warfarin was discontinued immediately; a therapeutic subcutaneous enoxaparin bridge was initiated.	Strict methodological requirement to prepare for accurate thrombophilia testing by preventing vitamin K antagonist-induced laboratory artifacts.
July 3, 2024	Targeted functional thrombophilia assays were drawn following an uninterrupted 14-day clearance of warfarin.	Unequivocally confirmed profound dual Protein C (26 IU/dL) and Protein S (13 IU/dL) genetic deficiency.
July 5, 2024	Enoxaparin bridge ceased. Transition to direct oral anticoagulant (Rivaroxaban 20 mg daily). Initiation of broad-spectrum oral antibiotics and topical corticosteroids.	Achieved predictable, targeted long-term anticoagulation that bypasses the natural pathway defect, coupled with source control of the regional inflammatory trigger.



Following the initial diagnosis, the patient was initiated on a long-term regimen of a vitamin K antagonist, specifically warfarin, targeting an international normalized ratio between 2.0 and 3.0. However, an analysis of the outpatient hematology records revealed a remarkably labile coagulation profile over the preceding six-month period. Despite the patient reporting strict adherence to the prescribed pharmacological regimen and demonstrating a consistent dietary intake of vitamin K-containing foods, his international normalized ratio fluctuated dangerously and unpredictably between 1.2 and 3.8. His past medical history was additionally notable for essential primary hypertension, which had been managed with calcium channel blockers, and a prior, recovering episode of central ataxia correlated with his initial cerebral insult.

Comprehensive physical and neurological examination

Upon presentation to the clinic, the patient's vital signs were comprehensively recorded. He was mildly hypertensive with a systolic blood pressure of 144 mmHg and a diastolic pressure of 99 mmHg. His resting heart rate was regular at 92 beats per minute, the respiratory rate was stable at 20 breaths per minute, and his core body temperature was normothermic at 36.2°C. A systematic physical examination revealed clear lung fields bilaterally and normal cardiac auscultation with no murmurs or gallops. Peripheral examination confirmed the complete absence of pitting or non-pitting extremity edema, and peripheral pulses were palpable and symmetrical.

A highly detailed neurological assessment was subsequently performed. Higher cortical functions, including orientation, memory, and speech, were fully intact. Cranial nerve examination from cranial nerve II through XII revealed no abnormalities; extraocular movements were full without nystagmus at rest, and facial sensation and motor functions were symmetric.

Motor examination demonstrated normal muscle bulk and tone, with full 5/5 strength maintained across all proximal and distal muscle groups in both the upper and lower extremities. Deep tendon reflexes were graded as 2+ and symmetric globally, with flexor plantar responses bilaterally.

Sensory examination confirmed the patient's subjective complaints, revealing a quantifiable, mild reduction to pinprick and light touch modalities in a stocking-glove distribution bilaterally in the lower extremities, consistent with early sensory neuropathy. Coordination testing demonstrated intact finger-to-nose and heel-to-shin performance, indicating an absence of appendicular cerebellar dysmetria. However, dynamic postural testing revealed a markedly positive Romberg sign; the patient exhibited significant truncal sway and required stabilization upon closing his eyes, pointing toward a profound central or proprioceptive vestibular deficit.

Diagnostic neuroimaging and otorhinolaryngological assessment

Given the patient's history of a prior dural sinus clot, the presentation of new, progressive neurological symptoms despite theoretical therapeutic anticoagulation necessitated an immediate and comprehensive radiological re-evaluation to differentiate between chronic post-thrombotic neurological sequelae and an acute failure of the antithrombotic therapy.

On June 12th, 2024, the patient underwent advanced neuroimaging. Magnetic Resonance Imaging of the brain utilizing T1, T2, fluid-attenuated inversion recovery, and gradient-echo sequences, performed concurrently with high-resolution Magnetic Resonance Venography with gadolinium contrast, yielded alarming results. The imaging sequences definitively revealed a severe, acute extension of the previously documented thrombosis. The newly formed, occlusive luminal defect involved the entirety of the superior sagittal sinus, the left transverse sinus, and



the left sigmoid sinus. Furthermore, the scan demonstrated distinct, acute antegrade propagation extending inferiorly into the proximal segment of the left internal jugular vein. Parenchymal evaluation demonstrated chronic ischemic changes localized to the deep periventricular white matter, classified as Fazekas grade I, accompanied by new, localized focal edema adjacent to the left transverse sinus, indicative of acute venous congestion.

During the systematic review of the extra-axial structures on the magnetic resonance images, a highly significant incidental otorhinolaryngological anomaly was detected. The imaging revealed extensive opacification within the paranasal cavities. To further characterize this localized inflammatory process, a dedicated, non-contrast CT-scan of the paranasal sinuses was immediately ordered. The CT-scan unequivocally confirmed the presence of severe, acute purulent pan-sinusitis. The radiological findings included massive, bilateral mucosal hypertrophy, complete obstruction of the osteomeatal complex, and distinct air-fluid levels within the bilateral maxillary, frontal, and ethmoidal air cells, alongside marked bilateral inferior nasal concha hypertrophy.

Laboratory investigations

Concurrent with the radiological evaluation, an exhaustive panel of hematological and biochemical laboratory investigations was drawn on June 12th, 2024. The complete blood count revealed a total white blood cell count of $7.84 \times 10^3/\mu\text{L}$, displaying a normal differential with neutrophils at $5.26 \times 10^3/\mu\text{L}$ and lymphocytes at $1.84 \times 10^3/\mu\text{L}$. The hemoglobin concentration was robust at 14.4 g/dL, with a corresponding hematocrit of 45.8 percent. Erythrocyte indices demonstrated a mean corpuscular volume of 92.5 fL and a mean corpuscular hemoglobin of 29.1 pg. The platelet count was adequate at $379 \times 10^3/\mu\text{L}$, ruling out consumption coagulopathy.

Renal and hepatic functions were completely preserved, which is a critical prerequisite for the

subsequent selection of renally and hepatically cleared anticoagulant therapies. The blood urea nitrogen was 5.8 mg/dL, and the serum creatinine stood at 0.87 mg/dL, yielding a highly optimal estimated glomerular filtration rate of 101.34 mL/min/1.73 m². Metabolic profiling confirmed optimal fasting glycemic control at 83 mg/dL, alongside a moderately dyslipidemic panel: total cholesterol 215 mg/dL, low-density lipoprotein 169 mg/dL, high-density lipoprotein 45 mg/dL, and triglycerides 159 mg/dL. Standard coagulation assays drawn upon admission returned an international normalized ratio of 2.24, an activated partial thromboplastin time of 33.1 seconds, and a prothrombin time of 30.1 seconds. Despite achieving this standard therapeutic ratio, the radiological confirmation of massive acute thrombus propagation confirmed a profound clinical failure of the warfarin regimen. Due strictly to the resource-limited setting of the treating facility, broad-spectrum autoimmune panels including antinuclear antibody and anti-double stranded DNA, alongside electroencephalography evaluation, advanced immunohistochemistry examination, and specific genetic testing for hypergammaglobulinemia and positive HLA-B genotyping, were omitted from the diagnostic workup. The clinical focus was instead directed toward actionable, high-yield diagnostic pathways.

The clinical team recognized a critical methodological barrier: accurate testing for underlying inherited thrombophilias, specifically the vitamin K-dependent natural anticoagulants, is scientifically invalid while a patient is actively consuming a vitamin K antagonist. To eliminate this severe diagnostic confounder, the patient was admitted to the inpatient ward and subjected to a strict pharmacological washout protocol. Warfarin was immediately discontinued. To maintain therapeutic anticoagulation during the clearance phase, the patient was transitioned to a weight-based, therapeutic subcutaneous bridge of low-molecular-weight heparin, specifically enoxaparin.



Following a mandatory, uninterrupted fourteen-day bridge, which ensured the total metabolic clearance of the vitamin K antagonist and the subsequent normalization of hepatic synthetic function, the patient's blood was drawn on July 3rd, 2024, for highly targeted functional coagulation assays (Table 2). The results of this rigorous methodological approach unequivocally confirmed a catastrophic, synergistic genetic failure: (1) Protein C functional activity: Markedly and dangerously reduced to 26 IU/dL against a normal reference range of 70 to 130 IU/dL; (2) Protein S functional activity: Critically depleted to 13 IU/dL against a normal reference range of 77 to 143 IU/dL.

Interdisciplinary clinical management and pharmacological transition

The definitive confirmation of a severe, dual genetic deficiency of the natural anticoagulant pathway, combined with the proven clinical failure of standard warfarin therapy and the acute prothrombotic trigger of severe pan-sinusitis, necessitated a comprehensive, interdisciplinary restructuring of the patient's management strategy. The neurovascular and hematology teams collaborated to safely transition the patient off the subcutaneous enoxaparin bridge directly onto a non-vitamin K oral anticoagulant. The direct Factor Xa inhibitor rivaroxaban was selected due to its predictable pharmacokinetics and its ability to bypass the defective Protein C and S pathways. It

was initiated at a fixed dosage of 20 mg daily. Simultaneously, the otorhinolaryngology service aggressively managed the localized inflammatory focus. The acute purulent pan-sinusitis was treated with a targeted, fourteen-day course of broad-spectrum oral antibiotics, combined with potent topical intranasal corticosteroids and saline lavages to reduce mucosal edema, facilitate sinus drainage, and eradicate the regional cytokine storm driving the secondary hypercoagulable state. To ensure comprehensive stabilization, the patient's adjunctive therapy was aggressively optimized. Phenytoin was continued at a dose of 200 mg every 12 hours to maintain a high seizure threshold and prevent secondary neuronal injury from symptomatic epilepsy. Cardiovascular risk factors were tightly controlled with the initiation of amlodipine 5 mg daily for hypertension and simvastatin 20 mg daily for the noted dyslipidemia. The patient demonstrated excellent clinical tolerance to the revised pharmacological regimen. Serial monitoring of quantitative D-dimer, a biomarker of active fibrinolysis and acute thrombosis, exhibited a profound and sustained therapeutic decline, dropping from an elevated baseline during the recurrence to a normalized value of 0.27 µg/mL. He was subsequently discharged with a schedule for rigorous outpatient clinical monitoring to ensure continued therapeutic efficacy and the complete absence of thrombotic recurrence.

Table 2. Longitudinal Laboratory Trends

Parameter	Baseline (Sept 2023)	Recurrence (June 2024)	Post-Washout (July 2024)	Post-Transition (Aug 2024)
D-dimer (ug/mL)	4.01	2.85	<i>Not Assessed</i>	0.27
International Normalized Ratio	1.10	2.24	1.05	<i>Not Monitored</i>
Protein C (IU/dL)	<i>Not Assessed</i>	<i>Not Assessed</i>	26	<i>Not Assessed</i>
Protein S (IU/dL)	<i>Not Assessed</i>	<i>Not Assessed</i>	13	<i>Not Assessed</i>



3. Discussion

The coagulation cascade is a finely tuned equilibrium between procoagulant forces and natural anticoagulant mechanisms.¹¹ The initiation of coagulation occurs via tissue factor exposure, which ultimately leads to the generation of thrombin via the prothrombinase complex. Protein C and Protein S are the primary gatekeepers preventing unchecked thrombin generation (Griffin et al, 2018). When thrombin binds to thrombomodulin on the intact vascular endothelium, it activates Protein C into Activated Protein C. Activated Protein C subsequently binds to its essential cofactor, free Protein S. This complex exerts profound anticoagulant effects by proteolytically cleaving and irreversibly inactivating two critical procoagulant cofactors: Factor Va and Factor VIIIa.¹²

In our patient, the severe quantitative reductions of both Protein C and Protein S represent a catastrophic failure of this inhibitory feedback loop. Without adequate Protein C to be activated, and without sufficient Protein S to act as a cofactor, Factors Va and VIIIa remain active for prolonged durations. This unabated enzymatic activity results in massive, unregulated thrombin generation. The presence of a dual deficiency exhibits a synergistic, rather than merely additive, prothrombotic effect, establishing a baseline of severe systemic hypercoagulability.¹³

A critical and often overlooked aspect of cerebral venous sinus thrombosis pathophysiology is the role of regional anatomical infections. The paranasal sinuses share a complex and direct venous drainage network with the intracranial dural venous sinuses via valveless emissary veins. This anatomical continuity allows for the direct propagation of localized inflammation and potential pathogens from the sinus cavities into the cerebral venous system.¹⁴

In this patient, the acute pan-sinusitis identified via CT-scan served as a powerful second hit in a genetically susceptible individual. Severe localized inflammation leads to the release of pro-inflammatory

cytokines, including Interleukin-6 and tumor necrosis factor-alpha, which directly induce endothelial dysfunction and upregulate tissue factor expression on the venous endothelium.¹⁵ This localized endothelial injury, combined with the profound systemic hypercoagulability caused by the dual Protein C and S deficiency, created a perfect storm for acute thrombus extension despite the patient possessing an international normalized ratio of 2.24 at the time of recurrence. Treating the sinusitis was therefore as critical as adjusting the anticoagulation therapy to halt the prothrombotic cascade.¹⁶

A major methodological pitfall in the diagnosis of inherited thrombophilias is the inappropriate timing of laboratory draws. Protein C and Protein S are vitamin K-dependent proteins.¹⁷ Warfarin exerts its anticoagulant effect by inhibiting the vitamin K epoxide reductase enzyme, thereby decreasing the hepatic synthesis of all vitamin K-dependent factors, including the natural anticoagulants Protein C and Protein S. Testing for these specific deficiencies while a patient is actively taking a vitamin K antagonist will inevitably yield artificially low results, making it impossible to distinguish between a true genetic deficiency and a drug-induced artifact. To ensure scientific and diagnostic rigor, our methodology required a complete cessation of warfarin and a fourteen-day bridge with low-molecular-weight heparin. Because low-molecular-weight heparin relies on antithrombin activation and does not interfere with vitamin K metabolism, it allowed the patient's intrinsic Protein C and S levels to return to their true genetic baseline before the functional assays were performed. This strict chronological approach validates the diagnosis of the dual hereditary deficiency in this case.¹⁸

The transition from warfarin to rivaroxaban in this case represents a critical therapeutic decision based on current pharmacological understanding (Figure 1). Warfarin's narrow therapeutic index and susceptibility to dietary fluctuations resulted in a highly labile



international normalized ratio, leaving the patient vulnerable to breakthrough thrombosis during subtherapeutic troughs. Rivaroxaban acts as a direct, competitive inhibitor of Factor Xa. Factor Xa is the critical convergence point of both the intrinsic and extrinsic coagulation pathways. For a patient with Protein C and S deficiency, where the primary pathophysiological defect is the inability to downregulate the pathway leading to Factor Xa and

thrombin, directly inhibiting Factor Xa bypasses the defective natural anticoagulant system entirely.¹⁹ Furthermore, direct oral anticoagulants possess highly predictable pharmacokinetics, allowing for fixed daily dosing without routine coagulation monitoring, vastly improving patient compliance and outcome stability. The sustained decrease in D-dimer levels to 0.27 ug/mL post-transition in our patient strongly validates the efficacy of this approach.²⁰

Pharmacological Paradigm Shift to Direct Oral Anticoagulants

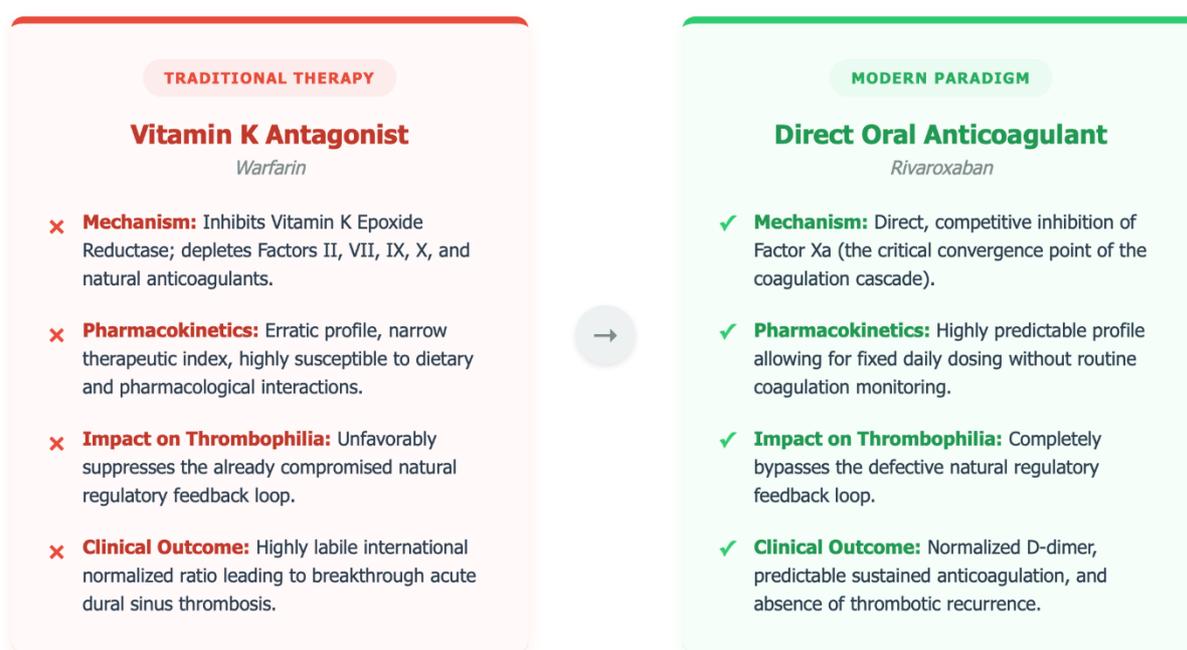


Figure 1. Pharmacological paradigm shift to direct oral anticoagulants.

A primary limitation of this study is its nature as an isolated case report, which restricts the generalization of the findings. While the transition to rivaroxaban proved highly successful in this specific instance of dual deficiency complicated by acute sinusitis, the broader efficacy of direct oral anticoagulants in the context of combined severe inherited thrombophilias remains an area requiring extensive study. Future research should prioritize multi-center prospective registries to establish

definitive, long-term recurrence rates and safety profiles for direct oral anticoagulants in rare genetic coagulopathies compared to traditional therapies.

4. Conclusion

Cerebral venous sinus thrombosis triggered by a concurrent hereditary deficiency of Protein C and Protein S is a complex medical emergency characterized by an aggressive hypercoagulable state. This case illustrates that a multidisciplinary



diagnostic approach, incorporating rigorous methodological timelines for thrombophilia testing to avoid medication-induced artifacts, is absolutely vital. Furthermore, the identification of acute pan-sinusitis highlights the critical role that regional inflammatory triggers play in precipitating acute thrombotic events in genetically vulnerable patients. The successful transition of this patient from a variable vitamin K antagonist to rivaroxaban demonstrates that direct oral anticoagulants offer a highly effective, predictable, and manageable long-term therapeutic strategy for patients harboring high-risk, multi-factorial inherited thrombophilias.

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