CASE REPORT

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Keywords:
cerebral venous thrombosis, elderly, hyperhomocysteinemia, mutation, venous infarction, an-ticoagulation, atypical stroke

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Contributions:
conceptualization: MM, CB; Clinical care and data collection: TM, MM; Writing: MM, CB. All authors approved the final version.
Conflict of interest:
the author(s) declare no potential conflict of interest.
Ethics approval and consent to participate:
not applicable.
Patient consent for publication:
obtained (written)
Funding:
none.
Availability of data and materials:
data and materials are available from the corresponding author upon request.

Received: 17 June 2025
Accepted: 24 June 2025

CEREBRAL VENOUS THROMBOSIS AND LIFE-THREATENING HYPERHOMOCYSTEINEMIA: A CASE REPORT OF MUTATION IN THE ELDERLY

ABSTRACT

Cerebral Venous Thrombosis (CVT) is a rare yet potentially devastating cause of stroke. Its highly variable and often atypical clinical presentation makes diagnosis challenging, particularly in the elderly where non-specific symptoms like confusion or depressed consciousness may predominate. Identifying the underlying prothrombotic condition is crucial for guiding secondary prevention.

We report the case of a 78-year-old woman presenting with acute, severe focal neurological deficits (left hemiparesis and global aphasia). Initial brain CT revealed a large hemorrhagic venous infarction in the left frontal-parietal lobes and subarachnoid hemorrhage, while CT-Venography confirmed superior sagittal sinus thrombosis.

The patient lacked classic CVT risk factors (e.g., malignancy, active infection, or oral contraceptive use). Comprehensive thrombophilia screening identified marked hyperhomocysteinemia associated with the homozygous C677T mutation as the sole identifiable prothrombotic cause.

The patient was successfully treated with therapeutic Low Molecular Weight Heparin (LMWH), transitioned to warfarin, and achieved a good neurological recovery despite initial complications.

This case underscores that CVT must be considered in the differential diagnosis of acute neurological deficits in the elderly, even with a misleading presentation (e.g., hemorrhagic infarction) and the absence of common risk factors.
Furthermore, severe hyperhomocysteinemia, stemming from the mutation, represents a significant and potentially reversible thrombotic risk factor in older adults.

Screening for hyperhomocysteinemia may be justified in unexplained CVT, regardless of age, as correction through folate supplementation can mitigate recurrence risk.

This article was published on December 30, 2025, at IJPDTM.IT
doi.org/10.30459/2025-40

RIASSUNTO

La Trombosi Venosa Cerebrale (TVC) è una causa di ictus rara ma potenzialmente devastante.
La sua presentazione clinica molto variabile e spesso atipica rende la diagnosi difficile, in particolare negli anziani dove possono predominare sintomi non specifici come confusione o stato di coscienza depresso. L'identificazione della condizione protrombotica sottostante è cruciale per guidare la prevenzione secondaria.

Riportiamo il caso di una donna di 78 anni presentatasi con deficit neurologici focali acuti e gravi (emiparesi sinistra e afasia globale).
La TC cerebrale iniziale ha rivelato un ampio infarto venoso emorragico nei lobi frontale-parietale sinistri e un'emorragia subaracnoidea, mentre la TC-Venografia ha confermato la trombosi del seno sagittale superiore.
La paziente non presentava i classici fattori di rischio per TVC (ad esempio, neoplasia, infezione attiva o uso di contraccettivi orali).

Uno screening trombofilico completo ha identificato una marcata iperomocisteinemia associata alla mutazione omozigote C677T come unica causa protrombotica identificabile. La paziente è stata trattata con successo con Eparina a Basso Peso Molecolare (EBPM) a dosaggio terapeutico, è passata al warfarin e ha ottenuto un buon recupero neurologico nonostante le complicazioni iniziali.

Questo caso sottolinea che la TVC deve essere considerata nella diagnosi differenziale dei deficit neurologici acuti nell'anziano, anche con una presentazione fuorviante (ad esempio, infarto emorragico) e l'assenza di fattori di rischio comuni. Inoltre, l'iperomocisteinemia grave, derivante dalla mutazione, rappresenta un fattore di rischio trombotico significativo e potenzialmente reversibile negli anziani. Lo screening per l'iperomocisteinemia può essere giustificato nella TVC inspiegata, indipendentemente dall'età, poiché la correzione tramite l'integrazione di folati può mitigare il rischio di recidiva.

INTRODUCTION

Cerebral venous thrombosis (CVT) is an uncommon type of stroke resulting from thrombosis of cerebral veins and dural sinuses. It affects predominantly younger individuals, especially women, and its presentation is often atypical in older adults [(1) (2)].
CVT may be associated with prothrombotic conditions, including hyperhomocysteinemia and genetic mutations such as MTHFR [(3) (4) (5)].
We report a case of life-threatening CVT in a 78-year-old woman without classic risk factors, in whom a homozygous MTHFR (Methylenetetrahydrofolate Reductase) mutation with severe hyperhomocysteinemia was the only identifiable cause.

CASE REPORT

A 78-year-old right-handed woman presented to the emergency department with sudden onset of left hemiparesis and global aphasia, preceded by a fall and right frontal cranial trauma. Her history included mild cognitive impairment, hypertensive cardiopathy, and osteoarthritis. She was not a smoker and was taking olmesartan, furosemide, quetiapine, and trazodone.
Neurological examination revealed severe hypotonic left hemiparesis (MRC 1/5 upper limb, 2/5 lower limb) and aphasia. Brain CT showed a hypodense lesion in the left frontal-parietal lobes with extensive hemorrhage.(**fig.1**)
Hyperdense material in the superior sagittal sinus and subarachnoid hemorrhage in the contralateral hemisphere were noted.
CT-angiography confirmed thrombosis of the superior sagittal sinus and collateral veins with right-sided predominance. (**fig.2**)

This article was published on December 30, 2025, at IJPDTM.IT
doi.org/10.30459/2025-40

Routine blood tests were normal, including inflammatory and infectious markers.
SARS-CoV-2 testing was negative.
The patient was admitted to the Stroke Unit and started on therapeutic Low Molecular Weight Heparin (LMWH), later switched to warfarin.
Thrombophilia screening revealed elevated homocysteine levels (91.8 µmol/L) and homozygous MTHFR mutation.
Other prothrombotic, autoimmune, infectious, and neoplastic conditions were excluded.
Neurological function progressively improved, with full resolution of aphasia and partial motor recovery.
The clinical course was complicated by left basal pneumonia and transient intestinal subocclusion, both resolved with conservative treatment.

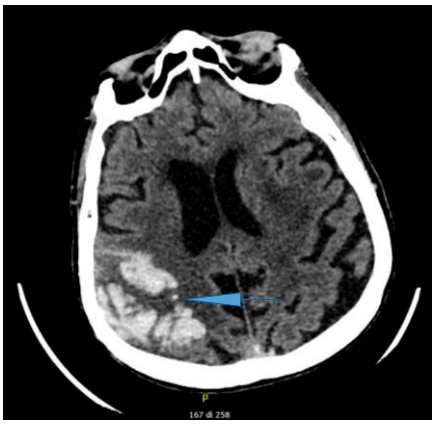

Fig. 1
Neuroimaging at admission revealed a hypodense lesion in the left frontal and parietal lobes, with extensive areas of intralesional hemorrhage.

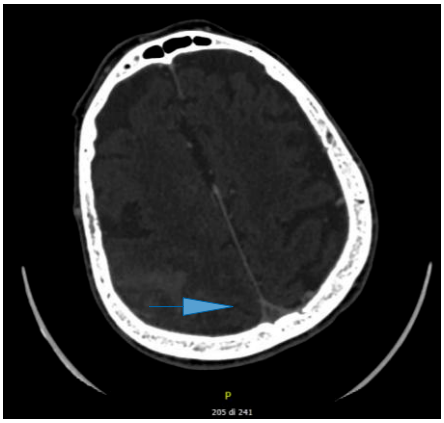

Fig. 2
The CT angiography confirmed thrombosis of the superior sagittal sinus and collateral veins, with right-sided predominance.

DISCUSSION

Cerebral Venous Thrombosis (CVT) accounts for a small percentage of all strokes () but carries a severe prognosis if the diagnosis is missed or delayed. Diagnosis is particularly challenging in older patients due to a distinct presentation pattern [(2)].
While younger adults often present with the classic triad of headache, seizures, and focal deficits, the elderly frequently exhibit atypical symptoms like depressed consciousness, mental status changes, or confusion[(1)]. These non-specific symptoms can easily be misattributed to metabolic encephalopathy, systemic infection, or a non-thrombotic stroke, significantly delaying the time to diagnosis [(3)].

In your patient, the absence of typical risk factors (e.g., oral contraceptive use, pregnancy) and the striking presentation with hemorrhagic infarction added another layer of complexity, potentially steering the diagnostic focus away from a venous etiology [(4)]. The presence of a hemorrhage with a low suspicion for CVT highlights the need for a high index of suspicion and prompt advanced neuroimaging, specifically MR Venography (MRV) or CT Venography (CTV), which remain the definitive diagnostic tools [(5)] [(6)] [(7)].

Anticoagulation in Hemorrhagic CVT: A Standard of Care
Despite the initial hesitation that a hemorrhagic component might create, anticoagulation remains the standard of care for acute CVT, including cases complicated by intracranial hemorrhage [(8)].
This counter-intuitive approach is justified by the underlying pathophysiology: the hemorrhage is typically secondary to venous congestion, not arterial rupture, and anticoagulation is necessary to prevent thrombus propagation and facilitate venous recanalization, thereby improving venous outflow and halting the hemorrhagic process.
The favorable outcome in your elderly patient, despite the hemorrhage, reinforces current guidelines.

It strongly suggests that advanced age and cerebral hemorrhage are generally not contraindications to prompt anticoagulation with parenteral heparin (often followed by a transition to Vitamin K Antagonists or DOACs for secondary prevention), provided that there are no other absolute contraindications[(9)].

This article was published on December 30, 2025, at IJPDTM.IT
doi.org/10.30459/2025-40

This case provides compelling evidence for the significance of the inherited thrombophilia in the context of advanced age.

1. **Hyperhomocysteinemia (HHcy) as an Independent Risk Factor**:
   Hyperhomocysteinemia is a well-established, strong, independent risk factor for CVT, increasing the risk by approximately four to seven-fold[10]. Elevated homocysteine damages the vascular endothelium, promotes oxidative stress, and alters platelet function, creating a highly pro-thrombotic environment in line with Virchow's triad [11].
2. **The C677T Mutation:**
   The common C677T mutation (especially in the homozygous state) results in reduced enzyme activity and, crucially, leads to elevated homocysteine levels, particularly when co-existent with folate deficiency. While the mutation alone may be a weak or controversial risk factor for thrombosis, the finding of severe hyperhomocysteinemia in this patient, secondary to the genetic defect, suggests a central etiologic role. This combination represents a high-risk pro-thrombotic state [12] [13].

The severity of hyperhomocysteinemia in patient underscores the need for thorough thrombophilia workup in all patients with CVT, irrespective of age or the presence of more common risk factors. The identification of this metabolic pathway defect (easily manageable with folate and B-vitamin supplementation) is paramount for guiding effective secondary prevention, which may prevent recurrent thrombotic events.

CONCLUSION

This case highlights the importance of considering CVT in the differential diagnosis of acute neurological symptoms in the elderly, especially when imaging reveals hemorrhagic infarcts.
Severe hyperhomocysteinemia due to MTHFR mutation may represent an underrecognized risk factor, even in the absence of traditional causes [14].

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This article was published on December 30, 2025, at IJPDTM.IT
doi.org/10.30459/2025-40