

Central Venous Sinus Thrombosis in a Young Woman Taking Norethindrone Acetate for Dysfunctional Uterine Bleeding: Case Report and Review of Literature

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Abstract

Background: The association between the progestin-only pill used for treatment of menstrual disorders and central venous sinus thrombosis (CVST) has rarely been reported in the literature. This report describes a case of central venous sinus thrombosis following intake of norethindrone acetate for dysfunctional uterine bleeding secondary to polycystic ovary syndrome in a young woman with undiagnosed underlying hyperhomocysteinemia.

Case: A 23-year-old woman presented with severe headache, followed by hemiparesis, seizures, and altered sensorium. She had been prescribed norethindrone acetate for the management of dysfunctional uterine bleeding secondary to polycystic ovary syndrome. Investigations revealed acquired hyperhomocysteinemia, presumably due to nutritional deficiencies, and evidence of CVST on MRI and magnetic resonance venography. Investigations showed no evidence of inherited thrombophilia. The patient was treated with low molecular weight heparin, followed by warfarin, vitamin B₁₂, vitamin B₆, and folic acid, and recovered successfully.

Conclusion: Although venous thrombosis is usually linked to the ingestion of estrogen, rather than progestogen, this case illustrates that patients who are prescribed progestogen-only pills for gynaecological disorders may develop thrombosis, especially if they have predisposing metabolic disorders.

présentant une hyperhomocystéinémie sous-jacente non diagnostiquée.

Cas : Une femme de 23 ans présentait de graves maux de tête, suivis d'une hémiparésie, de convulsions et d'une altération du sensorium. On lui a prescrit de l'acétate de noréthindrone pour la prise en charge de saignements utérins dysfonctionnels attribuables au syndrome des ovaires polykystiques. Les explorations ont révélé la présence d'une hyperhomocystéinémie acquise (vraisemblablement en raison de carences nutritionnelles) et de signes de TSVC (révélés par IRM et veinographie par résonance magnétique). Elles n'ont révélé aucun signe de thrombophilie héréditaire. La patiente a été traitée au moyen d'héparine de faible masse moléculaire, suivie de warfarine, de vitamine B₁₂, de vitamine B₆ et d'acide folique; elle a récupéré avec succès.

Conclusion : Bien que la thrombose veineuse soit habituellement liée à l'ingestion d'oestrogènes, plutôt qu'à celle d'un progestatif, ce cas illustre que les patientes à qui l'on prescrit des pilules ne faisant appel qu'à un progestatif pour contrer des troubles gynécologiques peuvent en venir à présenter une thrombose, particulièrement en présence de troubles métaboliques prédisposants.

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Résumé

Contexte : L'association entre la thrombose du sinus veineux central (TSVC) et l'utilisation de la pilule ne faisant appel qu'à un progestatif pour la prise en charge des troubles menstruels a rarement fait l'objet d'articles au sein de la littérature. Ce rapport décrit un cas de thrombose du sinus veineux central survenu à la suite de l'administration d'acétate de noréthindrone pour la prise en charge de saignements utérins dysfonctionnels attribuables au syndrome des ovaires polykystiques, chez une jeune femme

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INTRODUCTION

Central venous sinus thrombosis is an uncommon condition with a varied clinical presentation. A prothrombotic risk factor or a direct cause is identified in about 80% of patients with CVST.¹ However, even with extensive investigation, no cause is identified in 20% to 25% of cases. The various prothrombotic risk factors associated with CVST include genetically linked conditions such as antithrombin deficiency, protein C and protein S deficiency, factor V Leiden mutation, and hyperhomocysteinemia; acquired prothrombotic states such as nephrotic syndrome, antiphospholipid antibody syndrome, pregnancy, the puerperium, and oral contraceptive use; various inflammatory diseases such as systemic lupus

erythematosus, Wegener's granulomatosis, and sarcoidosis; and infections such as otitis, mastoiditis, and meningitis.¹ The Dutch Venous Sinus Thrombosis group prospectively compared data from a series of patients with cerebral sinus thrombosis with age-controlled population data. They found that 85% of women with a CVST used oral contraceptives, compared with 45% of women in the control group (age-adjusted OR 13). Among the women with a CVST, 19% had a prothrombotic tendency (which in the majority was a factor V Leiden mutation), compared with 7% expected in the population (age-adjusted OR 3.2). In women using a combined oral contraceptive who also had a prothrombotic abnormality, the OR for cerebral sinus thrombosis was 30.² However, an association between use of progestogen-only medication for the treatment of primary menstrual disorders and CVST has rarely been reported in the literature. We describe here the case of a young woman who developed CVST following prescription of norethindrone acetate for DUB secondary to PCOS and who was found to have acquired hyperhomocysteinemia.

THE CASE

A 23-year-old woman presented with sudden onset of severe headache associated with vomiting. This was followed six hours later by right-sided weakness and repeated episodes of generalized tonic-clonic seizures. She had been taking 5 mg a day of norethindrone acetate for DUB secondary to PCOS for the previous seven days. There was no history of fever, joint pain, rash, ear or nasal infection, or head injury. She was a non-smoker and had no personal or family history of venous thromboembolism, myocardial infarction, stroke, or diabetes mellitus. She was not taking any other drugs.

On examination, the patient was unconscious, afebrile, and pale, with pulse 100 beats per minute and blood pressure 150/90 mmHg. There was no cyanosis, clubbing, icterus, or

lymphadenopathy. Despite being unconscious, she moved the left half of her body in response to painful stimuli. There was no neck rigidity. Her pupils were equal and reactive to light, and she had bilateral papilledema.

A clinical diagnosis of CVST was made, and the patient was investigated accordingly. Apart from anemia (hemoglobin 8 gm/dL), no abnormality was noted in the hematologic profile, liver or renal function, serum electrolytes, coagulation profile, electrocardiogram, or chest X-ray. MRI of the head and MRV was performed. The MRI showed a wedge-shaped opacity involving both grey and white matter in the left frontal lobe. This lesion was hypointense on the T1W image and hyperintense on all other sequences. There was a mild midline shift (Figure 1). MRV demonstrated a loss of flow in the superior sagittal, straight and right sigmoid sinuses and multiple cortical veins compatible with a diagnosis of central cortical venous sinus thrombosis (Figure 2). In view of the CVST, thrombophilia screening was requested and the patient began treatment with LMWH in therapeutic doses. Mannitol was used as an anti-edema measure, and phenytoin sodium was used for recurrent seizures. The screening investigations for inherited thrombophilia, including protein C, protein S, and antithrombin III deficiencies, antiphospholipid antibodies (anticardiolipins IgG and IgM and lupus anticoagulant), factor V Leiden mutation, and prothrombin gene mutation, were negative. Serum homocysteine levels were elevated to 24.29 $\mu\text{mol/L}$ (normal 4.6–12.44). Screening for the methylenetetrahydrofolate reductase mutation was negative.

After completion of investigations the patient began treatment with vitamin B₁₂, vitamin B₆, and folic acid. Her antiepileptic treatment was changed to sodium valproate. After seven days of treatment she showed improvement and treatment began with warfarin sodium. After five days of warfarin therapy, the LMWH was discontinued and warfarin was continued to maintain international normalized ratio between 2.5 and 3.5. At follow-up one month later, she had no neurological deficit.

ABBREVIATIONS

CI	confidence interval
CVST	central venous sinus thrombosis
DUB	dysfunctional uterine bleeding
LMWH	low molecular weight heparin
MRI	magnetic resonance imaging
MRV	magnetic resonance venography
MTHFR	methylenetetrahydrofolate reductase
OR	odds ratio
PCOS	polycystic ovary syndrome
RR	relative risk

DISCUSSION

Central venous sinus thrombosis is a rare disorder, accounting for less than 1% of all strokes.³ It is more common in children and young adults.^{1,2} The estimated annual incidence of CVST is three to four cases per one million population and up to seven cases per million population among children.^{1,2} Seventy-five percent of affected adults are female.^{1,2} The most common signs and symptoms of CVST are severe headache (90%), seizures with or without secondary generalization (47%), hemiparesis (43%), papilledema (41%), impairment of consciousness at

Figure 1. Axial T2W MRI section showing venous infarct (arrow) in left frontal lobe with intermediate intensity thrombus in superior sagittal sinus anteriorly (arrow) with minimal midline shift.

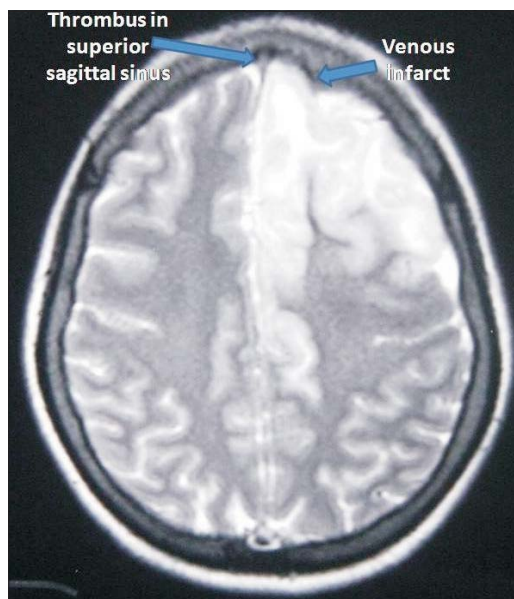
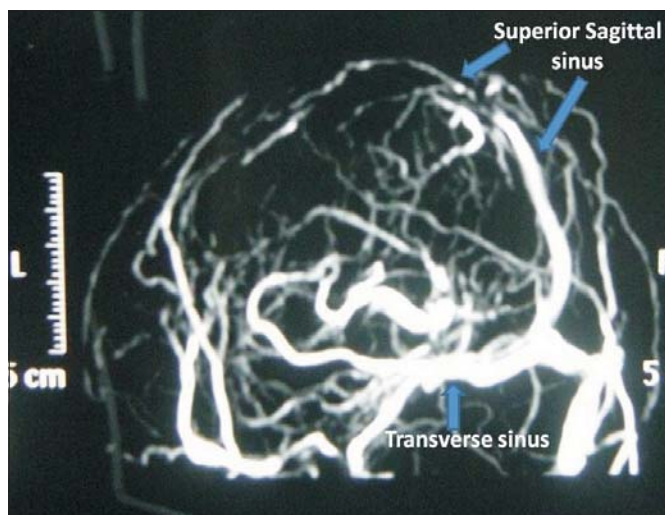


Figure 2. Maximal intensity projection (MIP) image of MRV showing thinning and irregularity of superior sagittal sinus anteriorly (arrow). Straight sinus is not visualized. These findings are suggestive of central venous sinus thrombosis.



presentation (39%), and coma (15%).² Twenty percent present with symptoms suggesting isolated intracranial hypertension (headache, visual disturbance, and papilledema).²

In the case described here, the patient had a history of progressively worsening headache after beginning to take norethindrone acetate for control of DUB. Two case-control studies have shown an increased incidence of sinus thrombosis in women who use combined oral contraceptives, especially third-generation oral contraceptives that contain gestodene or desogestrel.^{1,2} In fact, the development of headache with or without seizure in a young woman who has just begun using oral contraceptives should always alert the treating physician to suspect CVST.

Our patient was prescribed norethindrone acetate 5 mg/day for management of DUB. If a patient with DUB cannot take a combined oral contraceptive because of a history of thromboembolism, a progestin such as medroxyprogesterone 10 mg/day, norethindrone acetate 5 mg/day, or megestrol acetate 20 mg/day is often prescribed. An association between progestogen-only medication and an increased risk of CVST is not well-established. Data from the WHO collaborative study suggest that the use of progestogen-only preparations are associated with a significantly increased risk of venous thromboembolism (OR for current users vs. non-users 6.0; 95% CI, 1.19–30.3) but not stroke or myocardial infarction.^{4,5} In their study of 74 086 women, Vasilakis et al. showed that relative risk estimates for venous thromboembolism were 2.4 (95% CI 0.8–6.5) for progestin-only users, 3.4 (95% CI 0.8–13.7) for levonorgestrel-containing combined oral contraceptives, 8.0 (95% CI 2.1–29.9) for third-generation combined oral contraceptives, 6.5 (95% CI 1.6–27.1) for other contraceptives, 12.9 (95% CI 4.6–36.4) for pregnancy and the postpartum period, and 2.3 (95% CI 0.4–15.0) in postmenopausal women on hormone replacement therapy.⁶ This risk was compounded in smokers and in women with a body mass index greater than or equal to 25 kg/m².⁶ There was no effect when progestin-only preparations were used for contraception, but when they were used for primary menstrual disorders, a substantial association between progestin use and venous thromboembolism was found (RR 5.3).⁶ This probably was a result of the higher daily doses used for management of these disorders.

Our patient had been prescribed norethindrone acetate 5 mg/day for control of DUB; she had no evidence of thrombosis besides the CVST. Investigations subsequently disclosed that she had acquired hyperhomocysteinemia, presumably secondary to nutritional deficiencies. Epidemiological studies have shown that even mild hyperhomocysteinemia is associated with arterial and

venous thromboembolism. In a study of 45 patients with CVST, Cantu et al. found that hyper-homocysteinemia was associated with an increased risk of CVST (OR 4.6; 95% CI 1.6–12.8).⁷

Genetic and nutritional factors are important determinants of homocysteine metabolism. The common C6773T mutation in the MTHFR gene is associated with a thermolabile variant that has approximately one half normal activity. A positive result in genetic screening for both MTHFR wild type and MTHFR mutant suggests that the patient is a heterozygous carrier; a positive result for only MTHFR mutant suggests homozygosity for this mutation. In our patient, screening for a MTHFR mutation was negative. Conversely, because blood levels of folate, vitamin B₁₂, and (to a lesser extent) vitamin B₆ are related inversely to homocysteine levels, anyone with a deficiency of these vitamins is at increased risk of hyperhomocysteinemia. Various other causes of hyperhomocysteinemia include hypothyroidism, renal failure, leukemia, psoriasis, the postmenopausal state, and use of drugs such as methotrexate, nitrous oxide, isoniazid, phenytoin, and carbamazepine. Our patient had none of these conditions, and we presumed her hyperhomocysteinemia was nutritional in origin because she was also found to have anemia. We assume that an interaction between acquired hyperhomocysteinemia and progestin use in this patient resulted in CVST.

The treatment of choice for patients with CVST is anticoagulation with either unfractionated or low molecular weight heparin. The European Federation of Neurological Societies guidelines on the treatment of CVST state that concomitant intracranial hemorrhage related to CVST is not a contraindication to heparin therapy.³ A meta-analysis of three small randomized clinical trials assessing the effect of heparin treatment showed a non-significant reduction in risk of death or dependency (RR 0.46; 95% CI 0.16–1.31).⁸ The optimal duration of oral anticoagulation after the acute phase of treatment is unclear. Oral anticoagulation may be given for three months if CVST is associated with a transient risk factor, for 6 to 12 months if idiopathic CVST is associated with mild hereditary thrombophilia, and indefinitely if CVST occurs more than once or is associated with severe hereditary thrombophilia. There is insufficient

evidence at present to support the use of either systemic or local thrombolysis in these patients.⁹ Treatment to reduce cerebral edema, such as osmotic diuretics and hyperventilation, should be used only as critical interventions. Our patient was treated using these guidelines, and had a successful clinical outcome with use of LMWH followed by warfarin. Overall, more than 80% of all patients have a good neurological outcome if they are diagnosed and treated in timely fashion.^{3,8,9}

In summary, the present case emphasises the need for health care providers to consider the possibility of CVST in women who are prescribed the progestin-only pill and who present with severe neurological manifestations. Timely identification of such a complication will prevent increased morbidity and associated mortality.

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The woman whose story is told in this case report has provided signed permission for its publication.

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