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A CASE REPORT ON NORETHISTERONE INDUCED CEREBRAL VENOUS THROMBOSIS WITH VENOUS INFRACT IN LEFT PARIETAL LOBE

Vaishnav S. R.[1*], Anupama P. S.[2], Dr. Chitra C. Nair[3] and Dr. Beena P.[4]

[1,2]Pharm D Intern, KVM College of Pharmacy, Cherthala, Kerala.
[3]Professor and HOD, Department of Pharmacy Practice, KVM College of Pharmacy, Cherthala, Kerala.
[4]Principal, KVM College of Pharmacy, Cherthala, Kerala.

***Corresponding Author: Vaishnav S. R.**
Pharm D Intern, KVM College of Pharmacy, Cherthala, Kerala.

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ABSTRACT
Cerebral venous thrombosis (CVT) is a rare but potentially life-threatening condition with varied neurological presentations. Drug-induced CVT is uncommon, though oral contraceptives are recognized risk factors. Norethisterone, a synthetic progestogen, has been implicated in CVT development, though its role is not fully understood. A 46-year-old female presented with a 4-day history of headache, vomiting, and right-sided weakness and numbness. She had been on Norethisterone 5 mg daily and Tranexamic acid for abnormal uterine bleeding over the past month. MRI and CT imaging revealed dural venous sinus and cortical vein thrombosis with associated hemorrhagic infarcts. Laboratory investigations showed anemia, low MCV and MCH, and elevated WBC with neutrophilia. Thrombophilia screening was negative, ruling out inherited or acquired hypercoagulable states. A diagnosis of drug-induced CVT secondary to Norethisterone use was made, supported by imaging findings of thrombosis in the superior sagittal sinus, transverse and sigmoid sinuses, and cortical veins. The patient received anticoagulation (Enoxaparin and Rivaroxaban), antiedema measures, antiepileptics, steroids, diuretics, and antibiotics. She developed papilledema during hospitalization, which was managed successfully. Follow-up imaging showed stable findings. The patient improved clinically and was discharged after 15 days with no significant neurological deficits. This case emphasizes the need to consider drug-induced CVT in patients with neurological symptoms who are receiving progestogen therapy. Early diagnosis and prompt anticoagulation are critical for favorable outcomes.

KEYWORDS: Cerebral venous thrombosis, Norethisterone, Venous hemorrhagic infarct, MRI.

INTRODUCTION
Cerebral venous thrombosis (CVT) refers to the formation of blood clots in the veins that drain blood from the brain, including the cerebral veins and dural sinuses. Although it is an uncommon condition, CVT can result in substantial morbidity and even death.[1] The clinical presentation of CVT is highly variable and may include symptoms such as headaches, increased intracranial pressure (benign intracranial hypertension), subarachnoid hemorrhage, focal neurological deficits, seizures, unexplained changes in mental status, and meningoencephalitis.[2]

Cerebral venous thrombosis (CVT) has various underlying risk factors, including acquired conditions like surgery, trauma, pregnancy, cancer, and use of oral contraceptives, as well as genetic factors such as inherited thrombophilia. The Virchow triad—blood stasis, vessel wall changes, and blood composition changes—underpins CVT's pathogenesis. Prothrombotic conditions, such as deficiencies in antithrombin III, protein C, and protein S, and mutations like Factor V Leiden, are significant risk factors. Pregnancy, puerperium, and cancer, especially hematologic malignancies, also increase CVT risk. Other causes include infections, certain genetic disorders, and mechanical factors like lumbar punctures or epidural blood patches.[3]

Oral contraceptive use is strongly associated with an increased risk of cerebral venous thrombosis (CVT). A study in 1998 found that nearly all women with CVT were using oral contraceptives (96%), which increased the odds of developing CVT by 22.1 times. This risk is significantly higher in women who also carry genetic mutations like the prothrombin G20210A mutation or Factor V Leiden. In combination with these prothrombotic conditions, oral contraceptives further elevate the risk. Additional studies and meta-analyses support these findings, indicating that younger,

nonpregnant women with CVT often use oral contraceptives, particularly when genetic risk factors are present.[4]

The management of cerebral venous thrombosis (CVT) initially focuses on addressing life-threatening complications such as increased intracranial pressure (ICP), seizures, and coma. Seizure management includes anticonvulsant therapy and seizure prophylaxis if there is evidence of hemorrhage or infarction on neuroimaging. For increased ICP, elevating the head of the bed and administering dexamethasone and mannitol is recommended, followed by close monitoring in an ICU or stroke unit, with a neurosurgical consultation if needed. Once stabilized, treatment shifts to anticoagulation, and in some cases, thrombolysis or surgical thrombectomy.[5]

Anticoagulation aims to prevent thrombus growth, recanalize occluded veins, and reduce the risk of deep venous thrombosis and pulmonary embolism. Though controversial due to the risk of hemorrhagic transformation, evidence supports its use, especially with intravenous heparin or low-molecular-weight heparin as a bridge to oral anticoagulation. The target INR is 2.0–3.0, with duration depending on whether the CVT is provoked or unprovoked. In patients with severe thrombophilia or recurrent CVT, indefinite anticoagulation may be necessary.[6]

Thrombolysis, including both systemic and catheter-directed, is considered for patients with large, persistent thrombi who fail to improve with anticoagulation. While potentially beneficial in severe cases, the use of fibrinolytics carries an increased risk of intracranial hemorrhage. Surgical thrombectomy is an option for patients with significant neurological deterioration despite maximal therapy, especially when large infarcts or hemorrhages are present.[7]

Supportive care involves identifying and addressing any underlying risk factors, such as hormonal contraception or thrombophilia, and considering alternative contraception methods. Follow-up imaging is recommended 3 to 6 months after diagnosis to assess recanalization.

CASE REPORT

A 46 year Old female patient presented in emergency department with the chief complaints of headache, vomiting accompanied by numbness and weakness over right upper limb and lower limb developed 4 days before admission. The patient had history of abnormal uterine bleeding since 2 years ago and was on Tab. Norethisterone 5 mg 0-0-1 and Tab. Tranexamic acid for the last one month. The patient had no relevant family or social history. While on these tablet the patient developed severe headache and admitted to a nearby hospital. The Magnetic resonance imaging (MRI) Brain taken from that hospital was suggestive of dural venous sinus and cortical vein thrombosis and venous hemorrhagic infarct.

On examination, patient was afebrile with blood pressure of 140/80mmHg, Pulse rate of 79b/min, O2 saturation of 96% on room air. Patient was found to be conscious and oriented with GCS Score of 15/15 with a power of 4/5 in both right upper and lower limb.

Laboratory findings revealed Hb of 9.3 mg/dL (normal range 12-16g/dL), PCV- 31% (36-47%), MCV- 68fL(80-100fL), MCH-20Pg (27-32Pg), MCHC-30gm/dL(32-36GM/dL), RDW- 43.6%(11-16%), aPTT -2.5S(29-34S), PT-14S, INR -1.1, serum Na+- 134mEq/L (135-145mEq/L), TLC-18610c/mm(4500-11000c/mm), Neutrophils-85%(40-60%), Lymphocyte-13%(20-40%), Platelet count -323000/cmm (140000-440000/cmm).

Computed tomography (CT) scan of the head was obtained which suggestive of III defined hypodensity in left posterior frontal lobe and parietal white matter with control hyperdense foci-likely venous infarct with hemorrhagic transformation.

MRI brain was obtained and showed T1and FLAIR hyperintense thrombus in the cortical veins of the cerebral convexity, superior sagittal sinus, right transverse and sigmoid sinuses-s/o Cerebral venous thrombosis.

Other Relevant Laboratory Investigations

Thrombophilia Panel
Serum homocysteine:6.26 µmol/L(4.44-13.56µmol/L)
Protein S activity : 112% (55-123%)
Protein C activity: 120%(70-130%)
Antithrombin 3 antigen, Plasma by Nephlometry methode :27mg/dL (19-31mg/dL)
β2 glycoprotein I IgG: Negative
β2 glycoprotein I IgM: Negative
Cardiolipin antibody ACL IgG :Negative
Cardiolipin antibody ACL IgM :Negative
Protein S antigen (free) : 77% (71-113%)

The lab report were suggestive of drug induced (Norethistrone) CEREBRAL VENOUS THROMBOSIS She was treated with antiedema measures (Inj. Urob-G 100ml 1-1-1, Inj. Lasix 20mg 1-0-1), Antiepileptics (Inj. Brevipil 50mg 1-0-1), parental anticoagulants (Inj. Enox 40mg BD, Tab. Rivaroxaban 15mg BD), IV antibiotics (Inj. Ceftriaxone/sulbactum 1.5gm BD), steroids Inj. Dexamethasone 8mg BD, diuretics (Inj. Lasix 20mg BD, Tab. Diamox 250mg TDS and other supportive measures. After 5 days of admission complained of neck stiffness and papiloedema was managed with Tab. Diamox 250mg TDS.

Follow up CT scan performed on 6th day which showed no significant changes and MRI brain was repeated on 8th days of admission suggestive of venous infract with mild mass effect and hemorrhagic changes in left parietal

lobe. Dermatology opinion obtained for papular eruptions over face and neck. She was completely improved with stable vitals and discharged on 15th day.

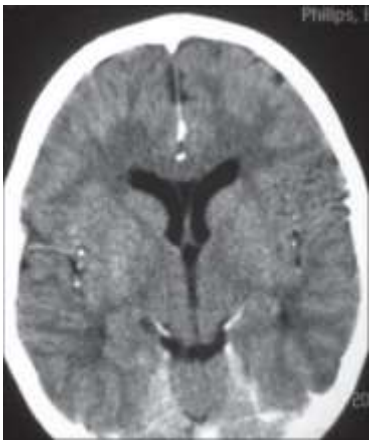

Figure 1: Plain CT of Brain showing III defined hypodensity in left posterior frontal lobe and parietal white matter with control hyperdense foci-likely venous infarct with hemorrhagic transformation.

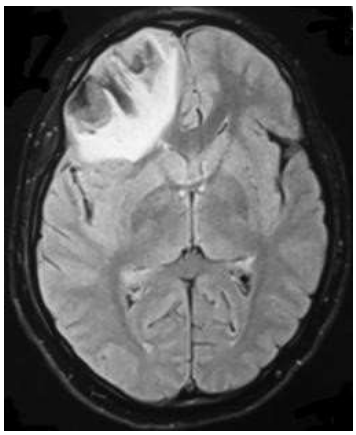

Figure 2: T1 weighted MRI brain showing right frontal hyper intense lesion with haemorrhage.

DISCUSSION

Cerebral venous thrombosis (CVT) is a rare but potentially life-threatening condition, particularly in young women. It is commonly associated with hypercoagulable states, dehydration, infections in adjacent areas, oral contraceptive use, hormone replacement therapy, pregnancy, and the postpartum period. CVST occurs more frequently in women than in men, with a female-to-male ratio of 1.29:1. While men exhibit a uniform age distribution, 61% of affected women are between the ages of 20 and 35.[5]

CVT typically presents with a severe headache, which is the most common symptom. Additional manifestations may include nausea, vomiting, seizures, altered consciousness ranging from drowsiness to coma, and focal neurological deficits.[2] Diagnosis relies on neuroimaging to detect the thrombosed vessel, with MRI brain combined with venography serving as the gold standard. The primary treatment approach involves anticoagulation, along with other recanalization procedures as needed.

Shortly after the introduction of the first combined oral contraceptive, a case of venous thrombosis linked to its use was reported. Since then, numerous observational studies have demonstrated that combined oral contraceptives (COCs) increase the risk of venous thrombosis by two to six times. Although the incidence of venous thrombosis among women of reproductive age is relatively low—approximately three cases per 10,000 woman-years—the widespread use of COCs makes their impact on thrombosis risk significant.[3-4]

Because ethinylestradiol, the estrogen component in COCs, was believed to contribute to the increased thrombosis risk, its dosage was progressively reduced. Early formulations contained 150–100 µg, which was lowered to 50 µg in the 1960s and further reduced to 30–35 µg and 20 µg in the 1970s. This reduction in ethinylestradiol dosage was associated with a decreased risk of venous thrombosis.[5-8]

In addition to lowering estrogen levels, modifications were made to the progestogen component to minimize side effects. Following the first-generation progestogens (norethisterone and lynestrenol), second-generation progestogens, such as levonorgestrel, and third-generation progestogens, including gestodene, desogestrel, and norgestimate, were developed. However, studies have shown that users of third-generation progestogens face a higher risk of venous thrombosis compared to those using second-generation formulations.[9]

Subsequent progestogens, such as drospirenone (introduced in 2001), have also been associated with an increased risk of thrombosis, exceeding that of second-generation progestogens in combined oral contraceptives.[9-10]

Although the risk of venous thrombosis increases with higher doses of ethinylestradiol, this effect appears to vary depending on the progestogen used. The reason for this interaction remains unclear, but one possibility is that different progestogens may vary in their ability to counteract the procoagulant effects of ethinylestradiol. Oral contraceptive use is known to elevate levels of coagulation factors II, VII, and VIII, as well as protein C, while reducing levels of antithrombin, tissue factor pathway inhibitor, and protein S. Clinical studies have shown that these coagulation effects are more pronounced in desogestrel users than in those using levonorgestrel, and they are specifically associated with combined oral contraceptives.[10-12]

It is important to note that all combined oral contraceptives increase the risk of venous thrombosis, unlike the levonorgestrel intrauterine device, which does not carry this risk. If a woman opts for combined oral

contraceptives, those with the lowest associated risk—such as formulations containing levonorgestrel with 30 µg of ethinylestradiol—should be preferred.

Homocysteine is a naturally occurring molecule involved in essential cellular reactions, leading to the formation of cysteine and methionine. If these pathways are disrupted due to genetic enzyme abnormalities or deficiencies in cofactors such as folic acid, vitamin B12, or vitamin B6, homocysteine levels may rise. Other contributing factors include chronic kidney disease, certain medications, smoking, and alcohol consumption.

Normal homocysteine levels range from 5 to 15 micromoles per liter. Elevated levels are linked to atherosclerosis and an increased tendency for blood clotting in arteries. While hyperhomocysteinemia has also been associated with venous thrombosis, including deep vein thrombosis and pulmonary embolism, its relationship with venous clots is weaker compared to its connection with arterial thrombosis.[12-15]

CONCLUSION

This case underscores a rare incidence of Norethisterone-associated cerebral venous thrombosis (CVT) in a 46-year-old female treated for abnormal uterine bleeding. The diagnosis was established through MRI and CT imaging, supported by negative thrombophilia screening, indicating a drug-induced etiology.

Timely initiation of anticoagulation, antiedema therapy, and supportive measures resulted in significant clinical improvement without lasting neurological deficits. This case highlights the need for vigilance regarding thrombotic complications associated with hormonal therapy and emphasizes the importance of early recognition and management to optimize patient outcomes.

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