

The Price of Transformation: The Startling Consequences of Excessive Estrogen on Transgender Health*

Leonaph Stephen Tumbaga, MD¹; Ainstein V. Misa, MD, FPRA²; Orstes Solis, MD, FPNA²

ABSTRACT

Cerebral venous sinus thrombosis (CVST) results from occlusion of cerebral venous sinuses, usually resulting in hemorrhagic infarction. It is a rare type of stroke affecting 3-5 per million people, often due to hypercoagulable states from clotting factor abnormalities or diseases like cancers, autoimmune and collagen vascular disease. Headache, visual changes, changes in sensorium, focal neurologic signs, seizures, and coma are some of the symptoms.

The role of exogenous estrogen in developing CVST among transgenders has not been reported frequently in literature. We report a 26-year-old transgender female who presented with throbbing headache after four years of exogenous high dose parenteral and oral estrogen. Magnetic resonance venography findings showed dural sinus thrombosis involving the left internal jugular vein, left sigmoid sinus, left transverse sinus, straight sinus, torcula and posterior aspect of the superior sagittal sinus. Patient was treated with topiramate, steroids and anticoagulants. Patient symptoms improved and was subsequently sent with home medications edoxaban. This case underscores the importance of monitoring the use of hormonal therapy in transgender individuals.

This report is an example of a rare cause of thrombosis secondary to self-administration of parenteral and oral estrogen. Prompt diagnosis in this patient resulted in the prevention of a catastrophic event like a major stroke, highlighting the importance of vigilance in managing hormone therapy. Increasing awareness about transgender issues can improve health and reduce inequities in this population. Cerebral venous sinus thrombosis (CVST) results from occlusion of cerebral venous sinuses, usually resulting in hemorrhagic infarction. It is a rare type of stroke affecting 3-5 per million people, often due to hypercoagulable states from clotting factor abnormalities or diseases like cancers, autoimmune and collagen vascular disease. Headache, visual changes, changes in sensorium, focal neurologic signs, seizures, and coma are some of the symptoms.

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This report is an example of a rare cause of thrombosis secondary to self-administration of parenteral and oral estrogen. Prompt diagnosis in this patient resulted in the prevention of a catastrophic event like a major stroke, highlighting the importance of vigilance in managing hormone therapy. Increasing awareness about transgender issues can improve health and reduce inequities in this population.

Keywords: Cerebral Venous Sinus Thrombosis, Estrogens, Transgender Persons, Venous System, Cerebral Sinuses, Thrombosis

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¹Region 1 Medical Center, Dagupan City, Pangasinan

² Adviser

INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is a rare disease with an estimated incidence of 3–5 cases per million population per year and accounts for a small proportion (1%) of all strokes ^(1–4). CVST is three times more common in women than men and affects the younger population (age <50 years) ⁽²⁾. Significant disability leading to dependency has been reported in about 5–10% of patients, and mortality rates range from 3 to 15% ⁽⁵⁾. The clinical presentation of CVST is divided into three distinct clinical syndromes: isolated intracranial hypertension (headache, papilledema, and visual disturbances), focal syndrome like seizures (39.3% cases), and paresis (37.2% cases) and encephalopathy in the form of altered mental status and coma ⁽⁶⁾. MR venography and CT venography have very high sensitivity and specificity to diagnose CVST.

Risk factors for CVST include inherited or acquired hypercoagulable states such as thrombophilias, neoplasms, autoimmune conditions and transient situations (such as pregnancy, post-partum period, surgery, trauma, dehydration, CNS infections)⁽²⁾. Hormonal medications including oral contraceptive pills (OCP), hormone replacement therapy (HRT), cross-sex hormone replacement therapy (CSHT), and other hormonal therapy have also been associated with venous thromboembolic events (VTE). Use of OCP has been shown in multiple observational studies to increase the odds of CVST by 5- to 22-fold ⁽⁷⁾. Data are insufficient to make conclusions about duration of use and other forms of hormonal contraceptives ⁽⁷⁾.

Transgender individuals have a gender identity that differs from the sex they were assigned at birth. Estimates of the number of transgender adults significantly increased over the past decade, with a current best estimate of 390 per 100 000 adults ⁽⁸⁾. That is about 1 in every 250 adults, or almost 1 million Americans ⁽⁸⁾. In the Philippines, recent data estimates it to be at

500,000 but challenges are still up to confirm this number ⁽⁹⁾.

Gender affirming healthcare is effective and medically necessary for those transgender individuals who seek it. Psychological, hormonal and surgical care for appropriately selected individuals has been unambiguously associated with improvements in gender dysphoria and decreased rates of psychiatric comorbidities. Hormone therapy describes the use of either steroid agonists, steroid antagonists and/or gonadotropin therapy to “masculinize” or “feminize” a patient. Adverse effects vary and depend on specific medication but include metabolic, electrolyte, renal, bone density effects, with possible cardiac events.

Structural inequities, refusal by providers, economic barriers, and non-access to hormone therapy has led many transgender individuals to pursue treatments through the internet or black market. The dangers and adverse effects of this misuse and non-medical or non-provider-mediated therapies are vast and include anaphylaxis, thrombosis, pulmonary hemorrhage, amputation, pneumonitis, and even death ⁽¹⁰⁾.

In the Philippines, where information on the health of transgender people is scarce, we aim to contribute and increase awareness of such issues by presenting this case to help address the inequities in this population

Objectives

- 1.) To present a case of cerebral venous sinus thrombosis in a transgender female with exogenous estrogen use.
- 2.) To increase awareness of the effects of exogenous estrogen use among transgender individuals.

CASE

J.D.V. 26-year-old transgender female, single, call center agent came in with a chief complaint of headache.

1 month prior to admission, patient had throbbing headache, 8/10 in severity, recurrent, relieved with intake of ibuprofen and paracetamol. No associated blurring of vision, dizziness, weakness nor fever. No consult was done.

1 week prior to admission, patient had increased frequency of headache, same intensity now occurring almost everyday. Patient was seen by an ophthalmologist and was told to have unremarkable findings. Patient then experienced photophobia and double vision thus was rushed to the hospital for admission.

Past medical history was unremarkable. She has hypertension and diabetes in the maternal side. No coagulation disorder in the family. Pertinent review of systems revealed alopecia, occasional oral ulcers, no joint pains, no rash. No history of head trauma.

For the personal and social history, she is an occasional alcoholic beverage drinker, non-smoker. Four years ago (2019), she started taking oral contraceptive pills and intramuscular injection of progesterone 50 mg plus estradiol benzoate 5 mg every 5 days. Two months prior to admission, she also started intramuscular injection of medroxyprogesterone acetate 50 mg plus estradiol cypionate 10 mg every 18 days.

Upon admission, physical examination revealed stable vital signs with blood pressure of 110/80 mmHg, a heart rate of 84 beats per minute, a respiratory rate of 20 cycles per minute, and an oxygen saturation of 97% in room air. Neurologic examination revealed no nuchal rigidity, no meningeal irritation. Extraocular muscle examination revealed L lateral rectus palsy. The

rest of the physical examination were unremarkable.

Initial impression was Idiopathic intracranial hypertension versus craniopathy cranial nerve VI, rule out central nervous system (CNS) infection. Patient was started on topiramate 50 mg/tab 1 tab OD, tramadol + paracetamol 1 tab TID as needed for headache and ceftriaxone 2 g IV OD. Laboratories were done and lumbar puncture was scheduled. Urinalysis, Covid 19 antigen rapid test and chest xray were all normal.

Table 1. Summary of blood tests

Blood test	Result	Reference range
White cell count	14.3	4.0–10.0
Hemoglobin	155	130–180
Hematocrit	0.48	0.40–0.54
Neutrophils	87.7	55.0–65.0
Lymphocytes	7.6	25.0–35.0
Eosinophils	0.3	2.0–4.0
Monocytes	4.2	3.0–6.0
Basophils	0.2	0.0–1.0
Platelets	515	150–450
SGPT	40	0–49
SGOT	24	0–46
Sodium	128.7	135.00–148.00 mmol/L
Potassium	4.26	3.50–5.30 mmol/L
Ionized Calcium	1.24	1.13–1.32 mmol/L
Creatinine	71.43	61.89–123.79 umol/L
Chloride	105.90	98.00–107.00
ESR	20	0–15 mm/hr
C-reactive protein	3	<1.0 mg/L
FT4	1.09	0.70–1.48 ng/dL
FT3	1.76	1.71–3.71 pg/nL

On the 2nd hospital day, lumbar puncture was done. Opening pressure was 9–10 cm and closing pressure was 9cm. Cerebrospinal fluid analysis revealed clear, colorless fluid, absence of any microorganism, negative for AFB, O WBC and RBC count. CSF glucose and protein were normal at 79.6 mg/dL and 12.12 mg/dL respectively. CSF India ink was likewise negative for encapsulated *Cryptococcus neoformans*. She was started on prednisone 20 mg/tab 1 tablet TID.

On the 3rd hospital day, patient still had headache. Topiramate increased to 100 mg/tab 1 tab OD. Patient was scheduled for MRI with contrast and MRA.

On the 5th hospital day, MRI and MRA with contrast were done which revealed dural sinus thrombosis involving the left internal jugular vein, left sigmoid sinus, left transverse sinus, straight sinus, torcula and posterior aspect of the superior sagittal sinus. She was started on enoxaparin 0.6 cc subcutaneously every 12 hours. Coagulation assay was requested. Patient was referred to rheumatology and infectious disease services.



Figure 1. Left transverse sinus thrombosis

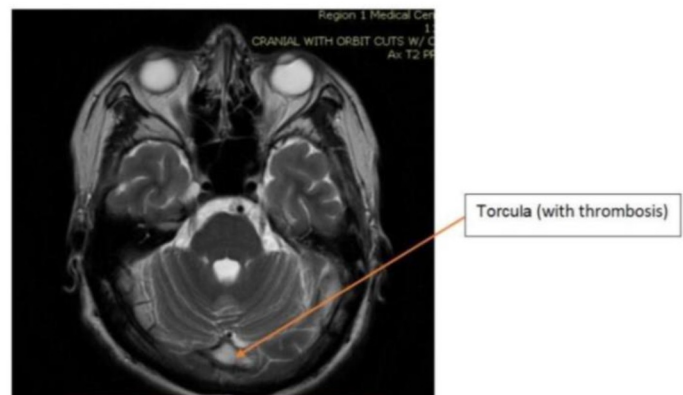


Figure 2. Torcula with thrombosis

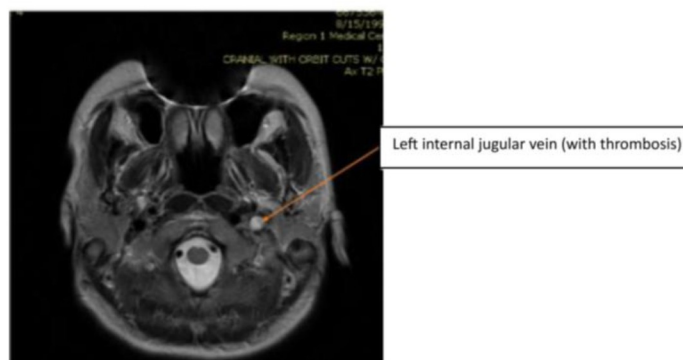


Figure 3. Left internal jugular vein with thrombosis

Normal right internal jugular vein, transverse and sigmoid



Figure 4. Normal right internal jugular vein, transverse sinus and sigmoid sinus on magnetic resonance venography

On the 6th hospital day additional tests like antinuclear antibody- immunofluorescence (ANA-IF), antiphospholipid antibody syndrome (APAS) panel, C3, anticardiolipin antibody IgG and IgM, anti- β 2 glycoprotein, human immunodeficiency virus (HIV) screening and rapid plasma regain (RPR) were requested and were all negative.

On the 7th hospital; day, severity of his headache decreased to 3/10. No new focal deficit elicited.

On the 8th hospital, started on oral anticoagulant (edoxaban 60 mg/tab 1 tab OD) to overlap with the enoxaparin.

On the 10th hospital day, headache was resolved. There was noted improvement of the left lateral gaze and decreased diplopia.

On the 11th hospital day, patient was discharged with improved symptoms and no headache. Advised to follow up with results of pending laboratories.

DISCUSSION

CVST is a particular type of cerebrovascular disease caused by complete or partial occlusion of the major cerebral venous sinuses ⁽¹¹⁾. The incidence of CVST has been rising with the advent of diagnostic techniques.

CVST can affect superficial cerebral veins, deep cerebral veins or dural venous sinuses. The isolated thrombosis of superficial cerebral veins is rare. The involvement of superficial veins is caused by the thrombosis of dural venous sinuses. About 60% of patients with CVST involve multiple dural venous sinuses, with the superior sagittal sinus the most frequently affected ⁽¹²⁾. These findings were consistent with the MRI venography of our patient except for the involvement of the internal jugular vein which is less common.

The International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) described the following as the most common presenting symptoms: headache (88.8%), seizures (39.3%), paresis (37.2%), papilledema (28.3%), and mental status changes (22%) ⁽¹³⁾. Similar to our patient, headache and paresis accompanied by diplopia were the presenting symptoms which prompted consult. Headache can be a feature of any site of cerebral venous occlusion, but is most prominent with larger sinus thromboses, such as sagittal sinus or straight sinus thromboses. Involvement of cranial nerve VI is usually bilateral and is secondary to the increased pressure within the cavernous sinus that compress the adjacent nerve, resulting in palsy or paralysis ⁽¹⁴⁻¹⁵⁾. The unilateral involvement in our patient further marks the rarity of this case which as of writing is the 7th case of such occurrence ⁽¹⁶⁾.

For the management, long-term anticoagulation is advised with the aim to prevent cerebral vein and sinus thrombosis (CVT) recurrence, which affects 2-7% of patients, and to prevent extracerebral venous thrombosis, which occurs in up to 5% of patients with CVT. In our patient, she is still on oral anticoagulant and was advised for repeat MRA.

The risk factor of our patient which led to CVST is the use of high dose parenteral and oral estrogen. Cross-sex hormone replacement therapy (CSHT) pursued by many transgender patients, allows individuals to develop secondary sex characteristics that conform to their gender identity. CSHT has been shown to improve transformation satisfaction, psychological profile, cognitive function, emotional repercussions, and quality of life in these patients and is typically continued lifelong ⁽¹⁰⁾. In the Philippines, we have yet to establish programs to address the needs of transgender individuals. Thus, most resort to treatments through the internet or by mere recommendations of friends and not by healthcare workers.

In a meta-analysis by Amoozeegar et. al, odds of developing CVST in women aged 15–50 years taking OCPs was 7.59 times higher compared to women not taking OCPs. Data are insufficient to make conclusions about duration of use and other forms of hormonal contraceptives. Oral contraceptive use and hormone replacement therapy were associated with an increased risk of stroke, especially during the first year of use, possibly due to immediate changes in hemostatic balance⁽¹⁷⁾.

Third-generation oral contraceptives are combined pills developed to reduce risk of cardiovascular disease due to their reduced androgenic activity. There is controversy as to whether third generation OCPs are associated with increased risk of venous thrombosis when compared to second generation OCPs. No definite recommendations can be made in favor of the safety of third generation OCPs when compared to previous generation OCPs in women with risk factors for developing CVST.

The increasing use of hormone therapy among transgender individuals without professional help will bring about more challenges in providing the best care for these individuals. In our patient, if diagnosis was delayed, catastrophic event like major stroke might not have been prevented.

CONCLUSION

This report is an example of a rare cause of thrombosis secondary to self-administration of parenteral and oral estrogen in a transgender female. The lack of data on transgender health limits knowledge about mechanisms for improving health and reducing inequities in these populations. Implementing policies that target the unique health needs of this population will create a more diversified research portfolio that will help illuminate the path toward health equity.

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