CASE REPORTS

CEREBRAL VENOUS SINUS THROMBOSIS WITH HEREDITARY ANTITHROMBIN III DEFICIENCY AFTER COVID-19 VACCINATION: A CASE REPORT

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Abstract

Hereditary antithrombin III deficiency is a prothrombotic disorder with an associated 50-90% risk of venous thrombosis. It rarely causes cerebral venous thrombosis in adults. Variable clinical presentations make the diagnosis a challenge. Careful clinical history, extensive clinical examinations, comprehensive investigations, and prompt management are necessary to save lives. COVID-19 vaccine-induced immune thrombotic thrombocytopenia may be a risk factor for cerebral venous thrombosis in these cases. Here, we are reporting an adult female with cerebral venous sinus thrombosis after receiving the COVID-19 vaccine. Subsequently, she was diagnosed with hereditary antithrombin III deficiency.

Keywords: *Cerebral Venous Sinus Thrombosis, Hereditary, Antithrombin III deficiency*

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Introduction:

Antithrombin III (ATIII) acts as an anticoagulant by inhibiting thrombin (factors IIa) and Xa. It is a non-vitamin K-dependent protease.[1] The deficiency of antithrombin III increases the chance of venous thrombosis.[2] Antithrombin deficiency is of two types, hereditary and acquired.[1] The prevalence of the hereditary AT III varies from 0.02 to 0.2 percent.[3] It is an autosomal dominant disorder.[4] About 50% of the heterozygous individual presents with thromboembolism.[5] The acquired causes of AT III deficiency include acute liver failure, cirrhosis, malnutrition, nephrotic syndrome, and malignancy.[1] This prothrombotic condition increases the risk of thrombosis in the cerebral venous sinus, especially in the presence of a provocating factor.[6] The isolated antithrombin III may account for 11.5% of cases of CVST.[7] Cerebral venous sinus thrombosis (CVST) is a potentially life-threatening condition that requires rapid diagnosis and urgent treatment. CVST presents with a spectrum of symptoms and signs.[8] Headache is the most prevalent (70-90%) of all symptoms, followed by hemiparesis, seizure, papilloedema, and unconsciousness.[7] CVST can be diagnosed with an MRI of the brain and MRV of the brain.[9] But the thrombophilia screening is the most important one to prevent a recurrence. The screening tests for thrombophilia include ANA, antiphospholipid antibody, protein C, protein S, antithrombin III, and factor V Leiden assay.[10] Heparin is the recommended first-line treatment for CVST, followed by 3–6 months of oral anticoagulation. However, a prothrombotic state warrants a long-term anticoagulant.[9] Here we are reporting a case who suffered two episodes of venous sinus thrombosis on different occasions (deep vein of leg and cerebral venous sinus) due to antithrombin III deficiency. The COVID-19 vaccine provoked cerebral venous thrombosis in this instance.

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Case Presentation

A 51-year-old female presented with headache, visual disturbances, frequent vomiting, and altered consciousness in a super specialized hospital. She was hypertensive, non-diabetic, postmenopausal, and overweight. There was no history of fever, cough, breathlessness, diarrhea, weight loss, joint pain, skin rash, lumps or bumps in the body, and trauma. She was diagnosed with deep vein thrombosis of the leg 25 years ago when she presented with a unilateral leg swelling during her pregnancy. Then she was treated accordingly without being evaluated for the etiology. Two months back, she received a second dose of the COVID vaccine. She was disoriented, and her GCS was 13/15. She did not have signs of meningeal irritations and focal neurologic deficit. Her Fundoscopic examination revealed bilateral papilloedema. The blood tests were within range except for low platelet, raised d- dimer and antithrombin III deficiency (Table 1). Chest X-ray and an ultrasound scan of the abdomen were unremarkable. CT scan head showed hemorrhagic infarct in the left parietotemporal lobe. MRI Brain with MR venogram revealed hemorrhagic infarct in left parietotemporal lobe with mass effect, with luminal narrowing, marginal irregularity at left transverse, sigmoid sinus, and internal jugular vein suggestive of partial venous sinus thrombosis (Figure 1, 2). She was treated with 7 days low molecular weight heparin (10 IU/kg of body weight) with complete in-hospital recovery. We repeated the antithrombin III 2 weeks after the discharge of the patient. The antithrombin III activity was 61%, which confirms the diagnosis of antithrombin III. She was discharged with tablet warfarin 7 mg, and her INR was 2.3 at discharge.

Table-I

Laboratory characteristics of patients on admission

Marker	Level	Reference
Hemoglobin	11.7 g/dl	13-17 g/dl
White blood cell	11200 mm3	4-11 × 10^3 mm^3
Neutrophil	9408 mm3	2-7.5 × 10^3 mm^3
Lymphocyte	1260 mm3	1.5-4 × 10^3 mm^3
Platelet	60000 mm3	150-450 × 10^3 mm^3
ESR	15 mm	0-12 mm
CRP	7 mg/L	< 10 mg/L
Serum Ferritin	87.34 ng/ml	20-300 ng/ml
D-dimer	3.27 µg/ml	<0.50 µg/ml
ALT	27 IU/L	10—40 IU/L
Random Blood Sugar	8.67 mmol/l	3.5-7.8 mmol/l
HbA1C	6.3 %	3.5-5.7 %
S. Creatinine	0.55 mg/dl	0.72-1.25 mg/dl
Prothrombin time	14 second	11-16 second
APTT	35 second	26-38 second
p and c ANCA	Negative	
ANA	0.328	<1.2
Anti-Cardiolipin Ab		
IgM	<2	< 15 U/ml
IgG	<3.15	
Protein C & S	140%	70-130%
Anti thrombin III	49%	80-120%
CA-125	5 IU/ml	< 45 IU/ml
Alpha Feto Protein	7 ng/ml	10-20 ng/ml
Serum Electrolyte		
Sodium (Na)	133 mmol/l	135-145 mmol/l
Potassium (K)	4.5 mmol/l	3.5-5.5 mmol/l
Chloride (Cl)	95 mmol/l	95-105 mmol/l
RT-PCR for COVID-19 from nasal swab	Negative	

CRP- C Reactive Protein, CA- Carcinogenic antigen, ESR- Erythrocyte Sedimentation Rate, ALT- Alanine amino transferase, APTT- Acivated partial thromboplastin time, ANCA- Antineutrophilic cytoplasmic antibody, ANA- Antinuclear antibody

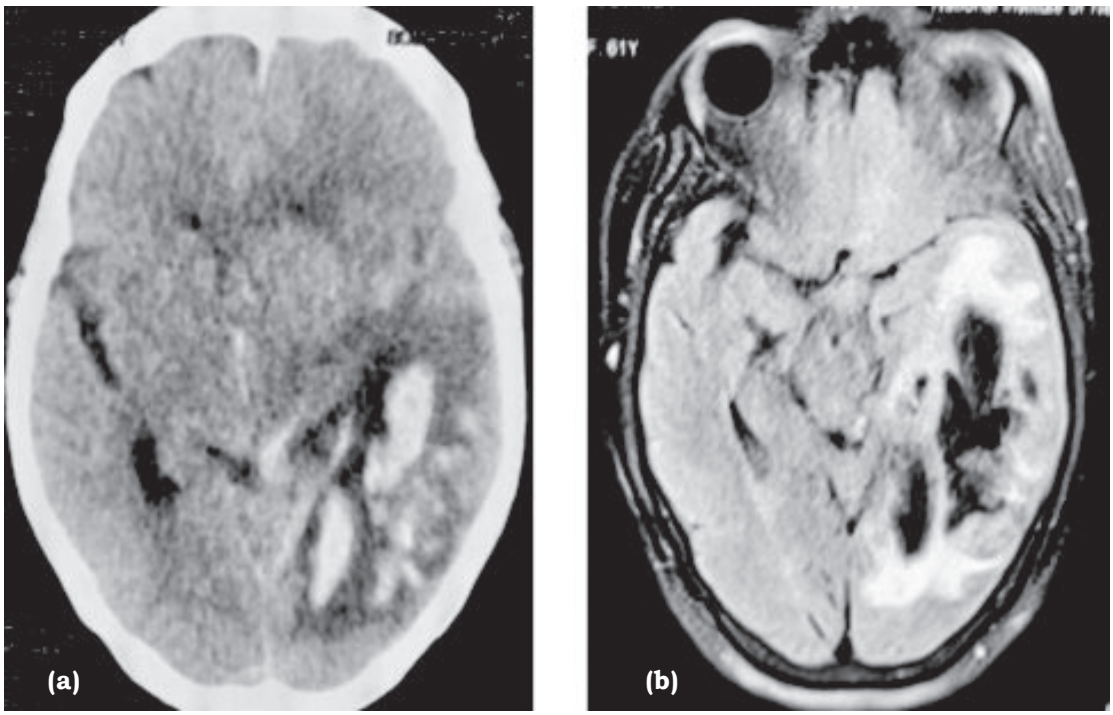

Fig.-1: *Imaging of the brain,* ***(a)*** *Non-contrast CT scan of the head showed a hemorrhagic infarct left parietotemporal lobe with perilesional edema,* ***(b) MRI*** *brain revealed hemorrhagic infarct in left parietotemporal lobe a uncal herniation.*

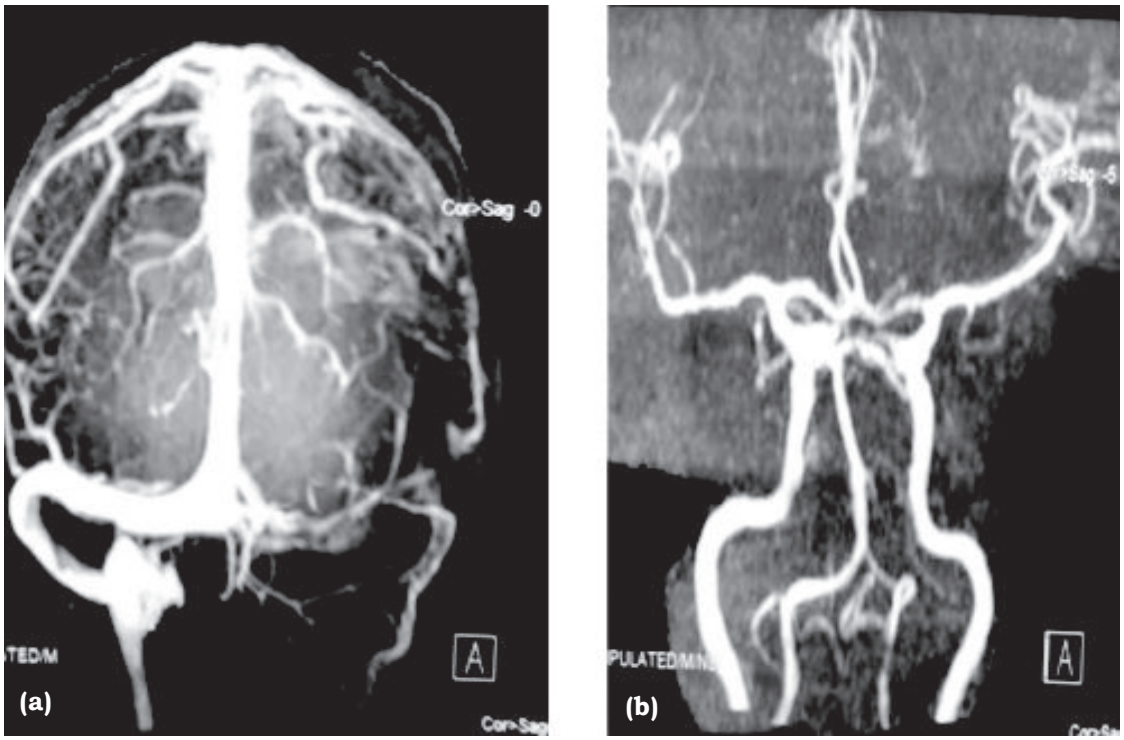

Fig.- 2: *MR venogram and MR angiogram of the brain,* ***(a)*** *MR venogram showing complete obliteration of left vein of Labbe, and luminal narrowing, marginal irregularity at left transverse, sigmoid sinus, internal jugular vein suggestive of partial venous sinus thrombosis (arrow)* ***(b)*** *MR Angiogram showing only hypoplastic left vertebral artery.*

Discussion

In this case report, we presented a case of recurrent venous thrombosis with antithrombin III deficiency in an adult. The last episode of thrombosis occurred after the COVID-19 vaccination.

This patient had a history of DVT during her pregnancy. But as pregnancy itself is a well-known risk factor[11] for DVT, she was not investigated for other causes. Now at the age of 50, she again developed venous thrombosis in the form of cerebral venous sinus thrombosis. In the hereditary deficiency of antithrombin III, thrombosis occurs unprovoked in 60% of instances. Whereas in 40%instances, it occurs due to transient risk factors.[12] In our patient, both incidences were provoked by transient risk factors, pregnancy, and the COVID-19 vaccine. Following the COVID-19 vaccination, cerebral venous sinus thrombosis occurs due to vaccine-induced immune thrombotic thrombocytopenia.[13] Low platelet count, high D-dimer level, and a high titer of antibodies to platelet factor 4 (PF4)-polyanion complexes are the diagnostic findings of vaccine-induced cerebral venous sinus thrombosis.[14] In this instance, we could not observe the antibody titer of PF4 due to limited facility. There are a few conditions where thrombocytopenia is associated with cerebral venous thrombosis. SLE is one of them.[15] Here, ANA was within range, and she developed thrombosis within two weeks of vaccination. So we concluded that the vaccine might be the risk factor for this instance. The acute stage of cerebral venous sinus thrombosis and ongoing heparin treatment may lower the antithrombin III activity.[16] So we confirmed the antithrombin III deficiency with a repeat test. The inherited antithrombin III deficiency is of two types, Type 1 and type II. Type I, there is the quantitative deficiency of antithrombin III. Type II, there is the qualitative deficiency of antithrombin III due to dysfunctional protein.[17] In this instance, as there was low antithrombin III activity, it is likely to be type I. We could no perform the genetic analysis due to a limited testing facility. The Hemorrhagic infarct was in the vein of Labbe territory, and in MRV of the brain, there was complete occlusion of the left vein of Labbe. The vein of Labbe thrombosis usually causes rapid deterioration due to uncal herniation.[18] In this case, there was uncal herniation. Our case was unique in two sense that history of deep vein thrombosis in pregnancy 20 years back, later again cerebral venous sinus thrombosis at the age of 50 after Covid vaccination. Another one was failure of prolongation of activated partial thromboplastin time after initiation of heparin. Heparin resistance has been described in some AT deficient patients, leading to inadequate activated partial thromboplastin time (aPTT) prolongation with heparin treatment.[19] As we started the treatment early with low molecular weight subcutaneous heparin, the patient recovered almost completely. According to recommendation [20], we continued low molecular weight heparin alone for five days, and then we started tablet warfarin 7 mg. The required INR 2.5 was achieved on day five after the initiation of the warfarin. So on day ten, we discontinued the heparin and discharged the patient with 7 mg warfarin to be continued for six months.

Conclusions:

We should be cautious in giving the COVID-19 vaccine to patients with a previous history of venous thrombosis. Each case of venous thrombosis should be screened for thrombophilia.

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Competing interests

The authors report no competing interests.

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