

Rare presentation of iron deficiency anaemia with cerebral venous sinus thrombosis in a middle-aged woman

Amna Bibi,¹ Chathuri Liyanapthirana,² Sajjad Khan¹

¹Department of General Medicine, East Sussex Healthcare NHS Trust, Saint Leonards-on-Sea, UK

²Department of Stroke, Eastbourne District General Hospital, Eastbourne, UK

Correspondence to

Dr Amna Bibi,
amnadalel@hotmail.com

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SUMMARY

This is a case of a female patient presented with a mild headache associated with recurrent episodes of nausea and vomiting, confusion and right-sided hemiparesis, diagnosed of haemorrhagic venous infarction from the thrombosis of left transverse and sigmoid sinus and probably the left vein of Labbe. She had severe microcytic hypochromic anaemia due to iron deficiency, without any other risk factors for cerebral venous thrombosis such as trauma history, infections, coagulation disorders or autoimmune diseases. She had a good prognosis after iron supplementation and anticoagulation therapy.

BACKGROUND

Cerebral venous thrombosis (CVT) is a relatively an uncommon cause of stroke, contributing <1%,¹ and the annual incidence is approximately 3 to 4 cases per million.²

It is three times more common among women than men.³ Asian and Middle Eastern countries have a relatively higher incidence of CVT than in other lands.⁴

It is multifactorial with several predisposing conditions. Patients usually present with non-specific symptoms such as seizures, headache, confusion, abnormal vision, vomiting, drowsiness and lethargy, make it difficult to diagnose.⁵

The risk factors include inherited hypercoagulable states, trauma, infection, dehydration, pregnancy and puerperium, neoplastic invasion of cerebral venous sinuses, haematological disorders and use of oral contraceptive (OC) pills. Although iron deficiency anaemia (IDA) has been reported as a cause of CVT in several paediatric cases, this association is extremely rare. To our knowledge,

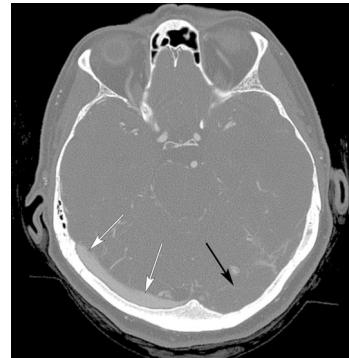


Figure 2 Brain CT venogram showing extensive filling defect left transverse sinus (black arrow). Normal right transverse sinus (white arrows).

IDA-associated CVT in adults has been rarely reported.

CASE PRESENTATION

A 63-year-old woman was admitted with sudden onset of headache, confusion, right hemiparesis and global aphasia. CT and subsequent CT venogram revealed left lateral temporal lobe venous infarction with haemorrhage and thrombosis of the left transverse sinus, sigmoid sinus, jugular bulb and the left vein of Labbe (figures 1–3).

The patient is a white British, with no family history of significance. There was no history of coagulation abnormality, recent trauma, autoimmune disease, hormonal substitution and gastrointestinal (GI) surgery. The only medication she took was over-the-counter paracetamol on an as required basis.

The laboratory tests revealed severe hypochromic microcytic anaemia with an initial haemoglobin value of 66 g/L (normal range: 125–165), a mean corpuscular volume of 57.8 fl (normal range: 80–100) and haematocrit of 0.227 (0.37–0.47) (table 1). Serum ferritin concentration was 7 µg/L (n=13–150). One study has shown that the most potent test for the diagnosis of IDA is the measurement of serum ferritin level.⁶ No B₁₂ vitamin or folate deficiency was found (table 2). Screening for coagulopathy was normal (table 2), including factor II, factor V (Leyden), activated protein C resistance and antiphospholipid antibodies. Protein C, protein S and antithrombin III were not interpretable because of early vitamin K antagonists therapy. Autoimmune profile and homocysteine levels were normal. Tissue transglutaminase antibodies were



Figure 1 Brain CT showing large posterior parietal and supratemporal venous infarct with haemorrhage (white arrows).

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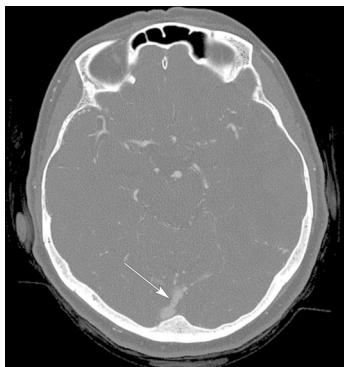


Figure 3 Brain CT venogram showing extensive filling defect left sigmoid sinus. Normal right sigmoid sinus (white arrow).

negative. Urine analysis did not show any blood. Upper and lower GI endoscopies, thoracoabdominal and pelvic CT were performed and failed to detect any malignant disease, source of active bleeding or pelvic vein thrombosis.

TREATMENT

The patient was treated by blood transfusion with packed red blood cells with target haemoglobin above 8 g/L, oral iron supplementation with ferrous sulfate 200 mg three times per day.

According to international guidelines, heparin is the basic treatment for CVT, irrespective of the presence of venous haemorrhagic infarct,^{5 7} with a good outcome.^{8 9} Therefore, our patient was started promptly on anticoagulation, initially infusion of unfractionated heparin, followed by oral warfarin for a total duration of 6 months. We did not start patient on non-vitamin K antagonist oral anticoagulants (NOACs) since there are no randomised trials that have examined their safety and efficacy in patients with CVT.

OUTCOME AND FOLLOW-UP

The patient's right hemiparesis gradually improved, as well as her global aphasia. The patient was discharged 1 month after the onset. The anaemia gradually improved with a haemoglobin value of 13.5 g/L on discharge, 6 weeks after the onset. Our assumption regarding the origin of the anaemia was a vegetarian diet without a proper iron substitution.

DISCUSSION

CVT is an uncommon condition and needs careful approach and consideration due to its potential morbidity.¹⁰ Because of its variable causes and predisposing conditions, delay in diagnosis is common. In one multicentre prospective study, 13.4% of patients had residual symptoms resulting in dependency, with a mortality rate of 8.3%.¹¹ Predisposing conditions for CVT are

Table 2 Blood tests results

Tests	Admission	Discharge	Normal range
INR	0.9	2.7	0.8–1.2
APTr	0.76	–	
Ferritin	7	40	13–150
Folate	6.1	–	3.9–26.8
Vit B ₁₂	232	–	197–771

APTr, Activated Partial Thromboplastin Time; INR, International Normalization Ratio; Vit B₁₂, Vitamin B12.

prior medical conditions (eg, thrombophilias, antiphospholipid syndrome, malignancy and inflammatory bowel disease), transient events (eg, surgery, pregnancy, puerperium, dehydration, infection and head trauma) and medications (eg, OCs, exogenous hormones and substance abuse).⁵

OCs result in a considerable increase in the risk of CVT in women of reproductive age and this risk is further increased when there is an associated prothrombotic condition.¹² However, there are studies showing that the use of OC resulted in the rise in the serum levels of ferritin and haemoglobin. The possible explanation is that the use of OC results in a reduced loss of menstrual blood.¹³

CVT in association with IDA is rare in adults, and there are only a few reported cases of CVT in association with IDA.^{14–17} However, one case-control study has shown a prevalence of 27% and a much stronger association.¹⁸ As compared with women, anaemia is more likely to cause CVT in men. The reason may be the discrepancy in the absolute incidence of CVT, which is two and half times higher in women.¹⁹ Also, men are more likely to have other risk factors causing anaemia such as recent surgery or infections.³ It was also suggested that in women, the use of OC could be the reason for the lower frequency of anaemia with CVT.^{20 21} However, a case-control study has shown that this is not a credible explanation.¹⁸

Some studies have shown a complication of pulmonary embolisms including fatal saddle embolism, resulting from the dislodging of emboli from the thrombosed superior sagittal sinus, with an overall incidence of 11.3% and a mortality rate of 95.6%.^{22 23} In one case report, a patient had both pulmonary embolism and CVT in association with IDA and has advocated a steady association between IDA and occurrence of CVT.²³

The exact mechanism for thrombosis in IDA is not known. The three elements of Triad of Virchow leading to thrombosis are: hypercoagulability, interrupted blood flow (stasis or turbulence) and damage to the vessel wall. In IDA, hypercoagulability and venous stasis play a major role in the formation of a thrombus.²⁴

The possible mechanisms by which IDA is suggested to cause thrombosis are: first, as iron is an important regulator of thrombopoiesis,²⁵ low iron levels disinhibit megakaryocyte activity,²⁶ which provokes secondary thrombocytosis, thus leading to a hypercoagulable state.²⁷ However, more often the platelet count remains below $700 \times 10^3/\text{mm}^3$.²⁸ Erythropoietin levels rise in IDA. Both thrombopoietin and erythropoietin have shown an analogy in an amino acid sequence, therefore, an increase in erythropoietin may result in an increase in platelet production.²⁹ Few studies have also reported that in secondary thrombocytosis, IL-6 levels were increased and, that, may be playing a pathogenic part in causing secondary thrombocytosis.³⁰ Some studies have also shown that IDA results in qualitative platelet abnormalities due to an increase in oxidant stress, and may augment aggregation of platelets.³¹

Table 1 Blood tests results

Tests	Admission	Discharge	Normal range
Hb	6.1	13.5	12.5–16.5
MCV	58	76.1	80–100
HCT	0.227	0.439	0.37–0.47
Platelets	560	457	150–400
WCC	7.91	4.61	4.0–11.0
RDW	17.6	17.6	11.8–14.8

Hb, Haemoglobin; HCT, Haematocrit; MCV, Mean Corpuscular Volume; RDW, Red cell Distribution Width; WCC, White Cell Count.

Another study has reported a comparatively normal platelet count in a third of patients with IDA, and thrombocytosis just a contributing element for thrombosis.³²

Second, microcytosis alters red cells deformability, which increases viscosity and possibly the risk of venous thrombosis.¹⁵ Third, low serum ferritin levels result in an increase in plasma concentration of coagulation factor VIII, hence increasing thrombosis risk.³³ Finally, anaemic hypoxia may occur as the oxygen-carrying capacity of erythrocytes decreases, especially in situations with increased metabolic demands in the brain and cause ischaemic damage in the area of the brain supplied by the terminal arteries. All these conditions lead to turbulent blood flow, causing platelets to come more frequently in contact with the endothelial lining.³⁴

A study has shown that the treatment of CVT with anti-coagulants is safe and may protect from further cerebral venous infarcts, worsening of neurological symptoms and pulmonary embolism.³⁵ Pulmonary embolism was one of the major causes of death in patients with CVT.²² According to the international guidelines, heparin is the keystone of the CVT treatment with good results.^{5 8 9} The safety profile of low-molecular-weight heparin is better than unfractionated heparin, however, unfractionated heparin is preferred when the patient is for urgent neurosurgical intervention and hence, a prompt reversal of anticoagulation is required.^{36 37} The two types of endovascular treatments (ET) for CVT³⁸ are mechanical thrombectomy and intrasinus thrombolysis; however, there are no major prospective or randomised trials on the efficacy and safety of ET; therefore, this treatment method is not in common practice. A small number of patients may develop herniation of subfalcine or transtentorial, and hence, merit quick neurosurgical intervention in the form of decompressive surgery (DS). Uncontrolled studies have shown good results of DS;³⁹⁻⁴² however, there are no randomised trials on the outcome of DS. NOACs, when compared with warfarin, have shown about 50% reductions in the relative risk of intracranial bleeds.^{43 44} However, apart from two minor case series,^{45 46} no randomised trial has examined the safety and efficacy of NOACs in patients with CVT.

Learning points

- Iron deficiency anaemia (IDA) can cause cerebral venous thrombosis (CVT).
- When cerebral infarction occurs, anticoagulation therapy with iron supplementation must be done immediately.
- Treatment for IDA may be an important strategy to prevent CVT and subsequent cerebral infarction.

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