

Cerebral Venous Thrombosis Secondary to Severe Iron Deficiency Anemia: A Case Study

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Summary

Cerebral venous thrombosis (CVT) has been associated with numerous etiologies and a myriad of symptoms. Although CVT in association with iron deficiency anemia (IDA) has been observed primarily in pediatric patients, very few cases have been reported in adults. Herein, we describe an encounter with a 28 year-old female who presented solely with a new onset headache due to transverse sinus thrombosis. Thrombophilia work-up was normal. She had no identifiable acquired causes of thrombosis. The patient demonstrated severe iron deficiency anemia secondary to myoma uteri causing menorrhagia.

Keywords: Cerebral Venous Thrombosis (CVT), Iron Deficiency Anemia (IDA), stroke, myoma uteri

1. Introduction

CVT is an uncommon type of stroke, which may account up to 0.5 to 1% of all strokes (Saposnik et al., 2011). Though definitive epidemiological studies on CVT are lacking, previous data suggests that it is rare (Saposnik et al., 2011; Ferro et al., 2001; Saadatnia et al., 2004; deVeber et al., 2001; Lanska & Kryscio., 2006; Kalbag & Woolf, 1967). Although CVT has been reported in adults, it has more commonly been observed in neonates and children in hospital-based studies (Ferro et al., 2004; Lancon et al., 1999). Furthermore, the ratio of adult females to males is 3:1 (Ferro et al., 2004; Coutinho et al., 2009).

CVT has a variable clinical presentation, requiring a high level of suspicion for diagnosis and management (Boussier et al., 1985; Masuhr et al., 2004; Saposnik et al., 2011). It has been found that two mechanisms may principally lead to the clinical features of CVT. The first is the thrombosis of cerebral veins or dural sinus leading to cerebral parenchymal lesions or dysfunction. The second being the occlusion of the dural sinus resulting in decreased cerebral spinal fluid (CSF) absorption and elevated intracranial pressure (ICP).

CVT has been classified into three syndromes based on signs and symptoms: (1) isolated intracranial hypertension syndrome (Biousse et al., 1999), (2) focal syndrome (focal neurological deficits and/or seizures), (3) encephalopathy (multifocal signs, mental status changes, stupor, and coma) (Ferro et al., 2001; Boussier & Russell, 1997). In addition, clinical symptoms of CVT may simulate neurological diseases like stroke, brain tumor, and encephalopathy (Huang et al., 2010). Although CVT may present with any of the aforementioned symptoms, the most frequent is headache (Saposnik et al., 2011).

Diagnostic imaging by MRI in combination with MRV is the single most sensitive technique for demonstrating CVT (Stam, 2005; Dormont et al., 1994; Lafitte, 1997; Connor & Jarosz, 2002; Liang et al., 2001; Wasay & Azeemuddin, 2005). Although MRA, 3D-CT, CT venography, and angiography are also alternative diagnostic studies (Volcy-Gómez et al., 2003; Saposnik et al., 2011). The need for invasive cerebral angiography is uncommon and reserved for inconclusive MRV and CTV results (Boussier, 2000; Lafitte et al., 1997; Yoshikawa et al., 2002). Although rare, deep CVT may also be challenging to diagnose due to its non-specific neuroradiological and clinical features (Huang et al., 2010). However, the most frequent location of CVT

includes the superior sagittal sinus (62%), followed by the lateral or transverse sinuses (41-45%) (Saposnik et al., 2011).

Overall, 80% of patients with CVT have a good prognosis (Ferro et al., 2004), especially when intracranial hypertension is the sole manifestation. In contrast, approximately 5% of patients die in the acute phase due to neurologic sequelae, most commonly brain herniation, whereas 10% of patients die secondary to long term sequelae. A poor prognosis is associated with deep CVT as well as altered mental status (Ferro et al., 2004; Azin & Ashjzadeh, 2008). The recurrence of CVT is relatively uncommon with rates of only 2-7% (Ferro et al., 2004; Gosk-Bierska et al., 2006). Treatment for CVT includes antithrombotic therapy as well as symptomatic treatments (Einhäupl et al., 2010; 2006).

CVT is multifactorial and has been associated with the following: inherited hypercoagulable state, myoma uteri, pregnancy, puerperium, cancer, head trauma, intracranial or systemic infections, vasculitis, inflammatory bowel disease, dehydration, oral contraceptives, substance abuse (Stam, 2003; Ferro, 2006), and Behcet's disease (Abdulkader et al., 1995). Review of the literature reveals very few cases of reported CVT secondary to IDA. We describe here in a case of transverse sinus thrombosis secondary to IDA in a young female patient as a consequence of myoma uteri and menorrhagia.

2. Case Report

A 28-year-old Asian female without significant comorbidity presented to our hospital with headache as the sole complaint for the past 2-3 weeks. The patient denied any history of previous migraines, chronic/recurrent headaches, recent head trauma, vomiting, or fever. However, a history of sporadic metro-menorrhagia with recent heavy menorrhagia during her last menstrual cycle was elucidated. The patient's hematologic work-up is illustrated in Table 1, it was consistent with iron deficiency anemia, additional laboratory values revealed serum iron of 6 µg/dL, TIBC of 572 µg/dL, transferrin of 400 mg/dL, and iron saturation of 1%. Celiac sprue studies were normal. Patient was subsequently transfused with 3 units of packed red blood cells and discharged home after hemoglobin returned to 11.2g/dL. The patient was referred to a gynecologist for further assessment and management. However, she returned to the hospital hours later due to a worsening headache.

She denied any neurological symptoms except severe headache, further neurological evaluation revealed no focal deficits. A CT scan revealed complete thrombosis of the left transverse sinus with associated parenchymal hemorrhage, either within the parietal lobe or the left posterior fossa, adjacent to the tentorium. MRI/MRV of the brain with and without contrast revealed confirmation of transverse sinus thrombosis (Figures 1a and 2a), with focal thrombosed tributary rather than intraparenchymal hemorrhage. After identifying the presence of thrombotic formation, etiological factors for thrombosis such as the use of oral contraceptives, family and personal history of thrombosis, pre-existing SLE and coagulation disorders such as factor V Leiden, prothrombin G20210A mutation, excessive factor VIII levels and PNH were ruled out. In addition, a coagulation panel was ordered revealing a PT of 12.0 seconds, and INR of 1.0, PTT of 25 seconds, and platelet count of 240,000 mm³ with additional normal laboratory values for anti-cardiolipin antibodies, B-2 glycoprotein I antibodies, antithrombin panel (AT), lupus anticoagulant panel (LAC), protein C and S, and homocysteine levels. During this hospitalization, a gynecology consult and imaging studies revealed the presence of myoma uteri, which was then surgically managed at a later time. She received intravenous iron to match her calculated iron deficit.

The patient was subsequently anticoagulated with heparin drip followed by warfarin daily until a therapeutic INR of 2.5 was achieved. Upon discharge, the patient was instructed to continue warfarin and oral iron therapy. Follow up MRV performed 8 weeks later demonstrated recanalization of the left transverse sinus. In addition, iron studies revealed a resolution of the anemia as shown in Table 1.

Table 1. Comparison of hematological values before and after treatment

Test	Normal Values	Before treatment	After Treatment
Hemoglobin	12.1-15.1g/dL	6.2 g/dL	13.3 g/dL
MCV	80-95fL	55 fL	95.3 fL
Ferritin	13-150 ng/mL	3 ng/mL*	135 ng/mL
Platelet count (Thousand/µL)	150-400	240	185

MCV=Mean Corpuscular Volume.

*Serum Ferritin is the most powerful test for the diagnosis of Iron Deficiency Anemia (Guyatt et al., 1992)

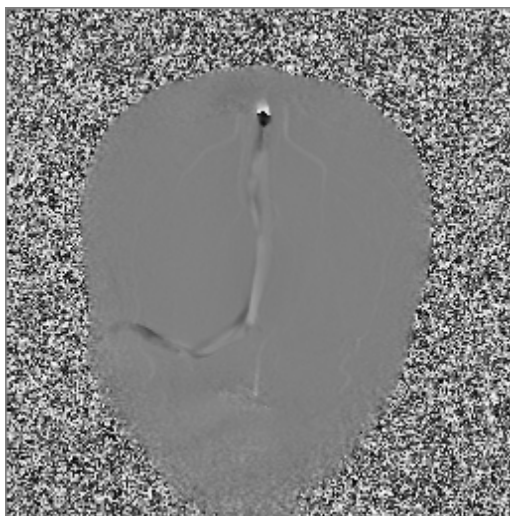


Figure 1a. MRV showing Left transverse sinus thrombosis

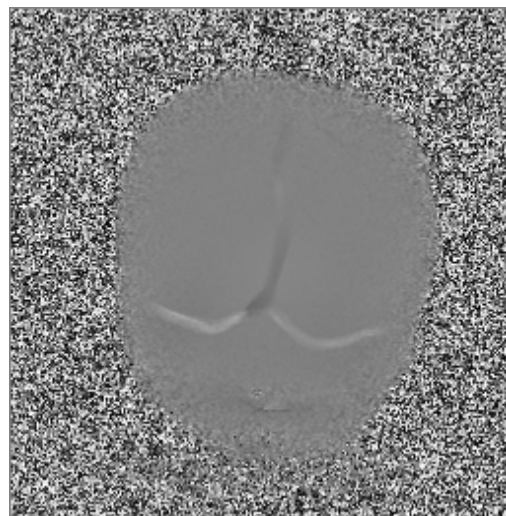


Figure 1b. MRV showing recanalization of left transverse sinus thrombosis after treatment

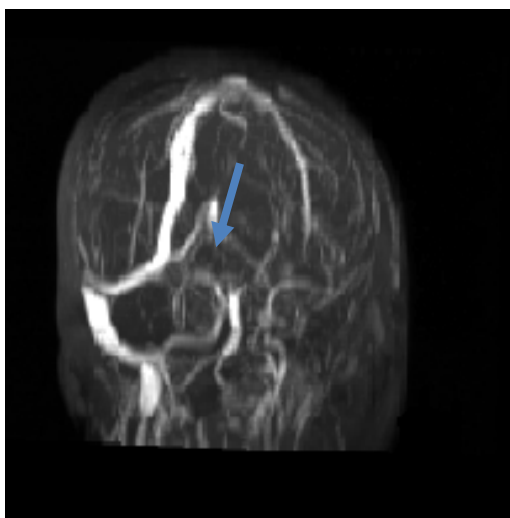


Figure 2a. MRV showing left transverse sinus thrombosis

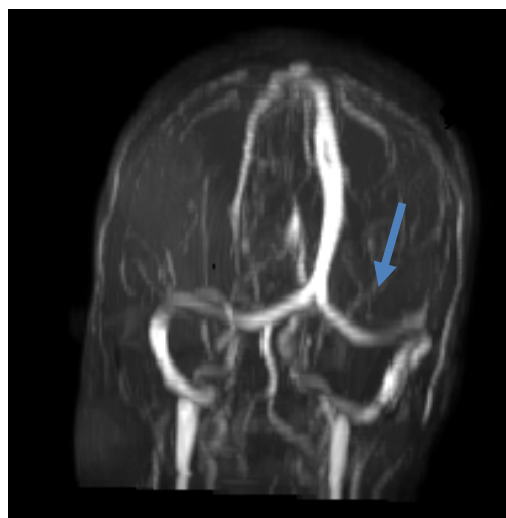


Figure 2b. MRV showing recanalization of left transverse sinus thrombosis after treatment

3. Discussion

CVT is an uncommon cause of stroke, which affects approximately five people per million per annum (Saposnik et al., 2011). As it is multifactorial, extensive investigations are often essential once the diagnosis is established. Around 85% of patients with sinus thrombosis may either have a prothrombotic risk factor or have an identifiable direct cause (Stam, 2005). As mentioned earlier, CVT can be associated with various risk factors, but CVT in association with IDA is extremely rare.

IDA is a worldwide problem and is relatively more frequent in children than in adults (Volcy - Gómez et al., 2003). Iron deficiency has been considered to be largely responsible for anemia, as circulating red blood cells have largest quantity of iron in the body (Cook et al., 1992). However, because of the role of iron in multiple processes at the cellular level (Yager & Hartfield, 2002), its deficiency can affect almost all organ systems including the brain. Neurological symptoms may include irritability, headaches, developmental delays (Yager, Hartfield, 2002; Hartfield et al., 1997) and, uncommonly, papilledema (Forster, 1985; Biousse et al., 2003), pseudo tumor cerebri (Parag & Omar, 1983), cranial nerve abnormalities like VI nerve palsy (Bruggers et al., 1990) and memory disturbances (Anezaki et al., 1992). Iron deficiency is seldom documented as an important trigger for stroke in children or adults (Hartfield et al., 1997).

To illustrate the relationship between IDA and CVT, the following mechanisms have been proposed:

(1) Thrombopoiesis is significantly regulated by iron (Karpatkin et al., 1974; Beguin, 1999), as normal quantity of iron is fundamental not only to maintain platelet production but also to prevent thrombocytosis. Thus, iron deficiency occasionally leads to thrombocytosis, which is associated with a hypercoagulable state. However, few cases of thrombocytopenia have been reported (Gupta & Joseph, 2001). According to Karpatkin et al., when iron deprivation occurs, it first leads to thrombocytosis; once the iron deficiency is severe enough to deplete iron, thrombocytopenia occurs (Karpatkin et al., 1974).

(2) Iron deficiency may also induce a hypercoagulable state by altering pattern of blood flow within the vessels due to decreased deformability and increased viscosity i.e. thickness of microcytic RBC (Hartfield et al., 1997).

(3) Low hemoglobin causes poor oxygenation. As a result, anemic hypoxia consequent to IDA could precipitate situations of increased metabolic stress predominantly in susceptible areas of the brain like basal ganglia and thalamus, due to end arterial blood supply (Balci et al., 2007). This fact could elucidate association of reversible focal deficits and stroke with IDA noticed by some authors (Hartfield et al., 1997; Young et al., 1983; Hart & Kanter, 1990).

Hypercoagulability, hemodynamic changes (either stasis or turbulence), and endothelial injury play important role in the thrombosis formation, according to Virchow's triad. Among these, hypercoagulability and stagnant flow predominate in thrombus formation in IDA (Ho et al., 2008). Although anemia causes increased arterial blood flow velocity (Aliefendioglu et al., 2007; Akins et al., 1996), it contributes to stasis in veins as a result of reduced deformability of microcytic RBC, which further leads to increased viscosity (Hartfield et al., 1997; Franchini et al., 2008). Intravascular thrombogenesis also caused by acute bleeding, as it augments platelet adhesiveness and reduces fibrinolytic activity (Ogata et al., 2008).

Although IDA commonly causes thrombocytosis, in our patient the number of platelets was not increased. To explain this association we have taken two studies into account:

(1) One study on iron deficiency and thrombosis reported that thrombocytosis is only a contributing factor for thrombosis as one third of cases had relatively normal platelet counts (Keung & Owen, 2004).

(2) Another study is a case control design by Stolz et al., in which data of a whole blood count and screening for thrombophilic coagulation abnormalities of 121 prospectively identified patients with CVT and 120 healthy controls were compared. In this study, severe anemia defined as hemoglobin <9 g/dl was independently and significantly associated with CVT of non-infectious origin, which might be interpreted as a higher dependence of hypercoagulability on the hemoglobin and hematocrit levels rather than on the extent of thrombocytosis. Despite the fact that this report did not specify the type of anemia and did not include the systemic analysis of iron metabolism, severe anemia was microcytic in 63% of cases with a female predominance. Hence, in most cases, iron deficiency anemia can be assumed (Stolz et al., 2007).

The association of IDA with sinus thrombosis has been reported previously in children (Sébire et al., 2005). However, only a few cases of adults with IDA have been reported (Balci et al., 2007; Ho et al., 2008; Ogata et al., 2008; Kinoshita et al., 2006; Aoki & Sakai, 1989). However, some of these cases were accompanied by other recognized risk factors of CVT, such as dehydration (Kinoshita et al., 2006), a hypercoagulable state (acquired protein C and protein S deficiency) (Ho et al., 2008), and cryoglobulinemia (Ho et al., 2008). These factors may have synergistic effects in addition to IDA and contributed to the CVT.

IDA is not a disease itself, but a manifestation of an underlying disease; Searching for the latter is therefore crucial and may be of far greater importance to the ultimate well being of the patient than just repleting iron stores (Rüfer et al., 2006). While the main cause of IDA in children is inadequate dietary intake or absorption, blood loss is the most common cause in adults. Blood loss could be due to hemoptysis, urine loss (hemoglobinuria, hemosiderinuria), gastrointestinal loss (parasites, ulcer, and malignancy), and from excessive menstruation. While the most common cause in adult men and post-menopausal women is GI blood loss, the commonest cause in pre- menopausal women is menstrual blood loss (Goddard et al., 2000). So far, two case reports have been published, wherein women with IDA presented with myoma uteri as a likely cause for CVT. One study reported hemorrhagic infarction in two women as a result of superior sagittal and transverse sinus thrombosis (Aoki & Sakai, 1989). Another study reported a woman with superior sagittal sinus thrombosis (Huang et al., 2010). These two reports as well as ours suggest that severe IDA secondary to myoma uteri related menorrhagia played a major role in the occurrence of CVT.

Although management of patients with CVT must be individualized, the basic therapy continues to be anticoagulation, which is intended to prevent propagation of thrombus and to increase recanalization. In all cases,

initial treatment consists of adjusted IV heparin dose or weight-based LMWH in full anticoagulant doses, followed by vitamin K antagonists, even with intracranial hemorrhage (ICH) (Einhäupl et al., 2010; 2006). Anticoagulation is not contraindicated for patients with intracranial hemorrhage that is resulting from CVT (Saposnik et al., 2011). In patients with transient risk factors, vitamin K antagonists may be continued for 3 to 6 months, to achieve the target INR of 2.0-3.0. Endovascular therapy i.e. thrombolysis or thrombectomy may be considered if anticoagulation is absolutely contraindicated or in case of initial treatment failure (Boussier, 2000; Masuhr, 2004; Stam, 2005). Steroids are not suggested, even with parenchymal brain lesions on CT/MRI if not warranted by another underlying disease (Canhão et al., 2008). For all patients therapy should be given for prevention of complications and symptomatic therapy should be given for seizures and ICP if present. Our patient received heparin and oral warfarin. The current initial therapy for patients with IDA is oral iron supplementation, which is inexpensive, nontoxic, and effective at correcting IDA. However, some patients do not tolerate it well, and in a subset of patients, it is insufficient, in which case parenteral supplementation is necessary (Wimbley & Graham, 2011). In this case, the patient was initially treated with intravenous iron followed by oral iron sulfate 325 mg TID, and was monitored with serial CBC and serum ferritin levels. Follow up MRI in our patient showed sinus recanalization (Figures 1b and 2b). However, in adults, limited data suggests that recanalization of the occluded sinus is not related to outcome after CVT (Strupp et al., 2002; Raizer & DeAngelis, 2000).

To summarize, this case suggests a connection between CVT and severe IDA, in this setting, iron deficiency should be considered as an underlying cause of CVT in not only pediatric population but also in adults. Despite the fact that in women of childbearing age, CVT can occur due to oral contraceptives, pregnancy and puerperium, special attention should be given to middle-aged women, as IDA is a predisposing disorder to sinus venous thrombosis. It is always important to look for menorrhagia, as they underestimate the extent of menstrual losses (McKenna et al., 1989). Recurrence of CVT could be significantly prevented by supplementation therapy for iron deficiency. Comprehensive treatment for IDA is required, as in the acute phase of CVT, anemia is frequently noticed as a relatively low hemoglobin (Hb) concentration (Sébire et al., 2005) and particularly in patients with other significant thrombotic risk factors should be treated actively.

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