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CASE REPORT

Prover Induced Cerebral Sinus Thrombosis in a SLE Patient

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Abstract

Cerebral vein and sinuses thrombosis (CVST) is a rare condition and accounts of 0.5-1% of all stroke. It is more common in women compared to men. Usage of oral contraceptive pill (OCP) has been recognised to increase the risk of developing CVST. We report a case of 46 Chinese lady with underlying systemic lupus erythematous (SLE) who presented with a second episode of sudden onset severe headache which secondary to CVST within 5 years. Both events were preceded by initiation of OCP (Provera) for her menstrual irregularities. Magnetic resonance imaging including venography and angiography (MRI/MRA/MRV) of brain revealed extensive dural sinus thrombosis which affect almost entire dural venous sinuses with preservation of the distal superior sagittal sinus. This case is discussed as it posed a diagnostic and management challenge as there were 2 major risk factors for this patient to develop CVST; OCP and active SLE. With early detection of the underlying cause of CVST, prompt treatment could have been initiated leading to a better outcome for this patient.

Introduction

Cerebral vein and sinuses thrombosis (CVST) accounts up to 0.5-1% [1] of all stroke. The estimated annual incidence is 3 to 4 cases per 1 million population and most of them are young to middle-age women, which accounts about 75% [2]. It is 3 times more common in women compare to men. Even though it is an uncommon, it may lead to acute neurological deterioration and severe morbidity and mortality. There are a few risk factors that are recognized to cause CVST, namely genetic and acquired pro-thrombotic conditions, inflammatory disease (e.g SLE, Behcet's syndrome), infections (e.g otitis media, sinusitis, meningitis), drugs (e.g contraceptive pill), head injury, dehydration and many more. One should consider of CVST in a young and middle age lady who presented with sudden onset of unusual headache or stroke like symptoms especially if there is evidence of intracranial hypertension or haemorrhage and patient who has no risk factors for vascular disease.

Here we report a case of 46 Chinese lady with underlying systemic lupus erythematous (SLE) who presented with second episode of CVST within 5 years after the first episode. Both events were preceded by initiation of Provera for her menstrual irregularities. Although CVST in SLE patient is uncommon and rarely reported, we still considered it as part of neurological manifestation of SLE. It usually present as an overlapping disease between vasculitis and neuropsychiatric lupus in SLE patient. In this case report, we will discuss the association between CVST and oral contraceptive use in SLE patient.

Case Report

This is a case of 46-year-old Chinese, female who has long standing systemic lupus erythematous (SLE) since 1989. She had multiple relapses predominantly autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia purpura (ITP) since the beginning of her disease which required prolonged glucocorticoid use. She is also on azathioprine. In September 2009, she had a history of severe headache without neurological deficit. CT brain showed left parieto-temporal-occipital hemorrhage with intraventricular extension into the left lateral ventricle and subarachnoid hemorrhage in the left occipital region. MRI, MRA and MRV of the brain showed left transverse/sigmoid sinus thrombosis with resultant hemorrhagic venous infarct at left temporo-occipital lobe. However, there was no evidence to support vasculitis. Her platelet level was within normal

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limit at presentation. Anticardiolipin antibody, Lupus anticoagulant and Anti-b2-glycoprotein I antibody were negative. On further history, she was started with oral contraceptive pill named Provera by gynaecologist for her irregular menstruation about 1 week prior to presentation. Warfarin was started and completed at 6 months. Repeated MRI/MRA/MRV brain 6 months later showed improvement of the thrombus with recanalization of the sinus.

She was doing well since the first stroke-like attack, except for the multiple ITP and AIHA relapses which requires adjustment of glucocorticoid. Unfortunately, she again presented with severe headache and vomiting in November 2014. There was no neurological symptoms reported. She was also started on provera for her irregular menses prior to current admission. Upon presentation, her GCS was 15/15, afebrile and hemodynamically stable. Her pupils reactive, 2 mm in size, bilaterally and no neurological deficit. Her Hemoglobin was 9.2 g/dL, white cell 6.9 × 10^9/L and platelet 269 × 10^9/L. MRI, MRV brain revealed extensive dural sinus thrombosis which affect almost entire dural venous sinuses with preservation of the distal superior sagittal sinus.

In view of this new cerebral sinus thrombosis, she was started on subcutaneous enoxaparin 60 mg twice daily and also adequate analgesic for her persistent headache. Prednisolone was continued at old dose which was 30 mg (she was recently had AIHA and prednisolone was adjusted). However, at day 6 of admission, she developed first episode of self-aborted generalised tonic clonic seizure, lasted about 5 minutes. Repeated CT brain showed new area of infarct and frontal hemorrhage with perilesional edema.

Since this patient is case of SLE, it was difficult to decide whether this neurological presentation is mainly due to cerebral lupus or provera-induced. Furthermore, her SLE is active as evidence by low C3/C4 with recent relapse of AIHA thus making cerebral lupus high on the list of suspicion. In view of this consideration, she was given glucocorticoid pulse therapy and followed by maintenance dose. The anticoagulation was also continued and fortunately, she recovered well.

Discussion

Cerebral venous sinus thrombosis (CVST) is the presence of thrombus in the dural venous sinuses and may cause stroke. Although it accounts to about 0.5% [1] of all stroke yet it can lead to fatal neurological deterioration. There are multiple risk factors which have been associated with CVST and not all are reversible. These risk factors can be divided into acquired and genetic. Examples of acquired risks are including the following of head trauma or surgery, pregnancy or puerperium, antiphospholipid syndrome, infections, inflammatory disease (e.g SLE, Behcet's disease), cancer or oral contraceptive use and many more. Genetic risks include inherited thrombophilia such as antithrombin deficiency, Protein C or S deficiency and Factor V Leiden mutation.

Two different mechanisms are involve in the pathogenesis of CVST; cerebral vein thrombosis and major sinuses thrombosis. Commonly, both mechanisms occur simultaneously. In cerebral vein thrombosis, venous obstruction lead to formation of local effect such as localised cerebral edema, venous infarction and petechial hemorrhage. The latter can become large hematoma as well. Two types of cerebral edema that have been identified in CVST namely cytotoxic edema and vasogenic edema [2], as proven by magnetic resonance imaging (MRI) [3,4]. Basically, cytotoxic edema is due to ischemia which damage the energy dependent cellular membrane pumps leading to intracelullar swelling while vasogenic edema is due to disruption of blood brain barrier and leakage of blood plasma into interstitial space [2]. Fortunately, vasogenic edema is reversible if the underlying cause is treated well. In major sinuses thrombosis, the venous occlusion cause raised in intracranial pressure by increasing the venous pressure and impaired the absorption of cerebrospinal fluids.

Previously, both female and male were equally affected of CVST. However, after recent years of introduction of oral contraceptive, there is a significant different between these two gender group where 70-80% are in women of childbearing age [5]. Two case-control studies have shown an increased risk of sinus thrombosis in women who use OCP [6,7]. The different is about sevenfold when compared to non-OCP use. It is thought that the most common cause or risk for CVST is due to prothrombotic state cause by certain condition such as antiphospholipid syndrome, pregnancy or nephrotic syndrome. Study from Vandenbroucke, et al. revealed that there is prothrombotic effect of OCP based on laboratory finding which explained why CVST mostly affected childbearing age women [8].

SLE is an inflammatory (autoimmune) disease and identified as one of the risk factor for development of CVST. Not many CVST in SLE has been reported due to its rarity with the incidence only about 0.36% [9]. It is usually present as an overlap disease between vasculitis and neuropsychiatric lupus (NPLE) in SLE patient. There are few risk factors that have been identified to cause CVST in SLE patients. The formation of vasculitis caused by immune complex deposition on endothelial lining [9] play a major role in this disorder thus causing NPLE as well as CVST due to venous thrombosis. Antiphospholipid syndrome should also need to be considered as risk factor for CVST in SLE patient [10]. As we know, chronic use of glucocorticoid and other immunosuppresion in SLE patient potentially cause infections, and in CVST, infections of middle ear, facial skin or intracalvarium are common causes [2]. Other than that, complication such as hypoalbuminemia with nephrotic-nephritic syndrome in Lupus nephritis could represent another risk factors [11].

Combination of Magnetic resonance imaging and magnetic resonance venography do help in identifying and confirming the thrombosis, although expert radiologic judgment is needed to avoid pitfalls. Magnetic resonance imaging also help to differentiate between arterial and venous cause of stroke-like symptoms. MRI of the brain may show presence of hyperintense signal from the thrombosed sinus, while MRV will show absence of flow within the thrombosed sinus thus confirming the diagnosis [12]. However, thrombus in smaller sinus such as cortical vein may be impossible to identify and the local effect cause by this CVST may be mistaken for others, such as space occupying lesion or demyelinating. MRI brain also may identify area of hemorrhage or infarction as the consequence of the thrombosis which may help in determining the prognosis as well as the extend of the management.

Regardless of the underlying cause of CVST, the principal treatment should include i) Removal of precipitating factors and treat the underlying disease; ii) Anti-thrombotic therapy such as warfarin; iii) To reduce the intracranial pressure and vi) To reduce neurological symptoms. As CVST secondary to active SLE cannot be rule out in this case, and it is known that this disease has high SLE activity with rapid disease progression, glucocorticoid pulse therapy (followed by maintenance) should be considered in order to achieve clinical remission as soon as possible [9], and of course the oral contraceptive should be withdrawn. Initiation of anticoagulant remain the cornerstone of the treatment of CVST. This treatment not only to facilitate recanalization but to prevent further thrombus and to prevent deep venous thrombosis or pulmonary embolism [13,14]. However, there is some controversy especially whether it is safe to use if CVST is complicated with cerebral infarction with hemorrhagic transformation as 40% of patients with CVST have hemorrhagic transformation even before the therapy. One should know that, even in the absence of anticoagulant therapy, acute CVST with hemorrhagic transformation carries adverse outcome and associated with high mortality [13]. Although Meta-analysis of 2 randomised controlled trials comparing between anticoagulant therapy and placebo during acute phase revealed non statically significant reduction in relative risk of death or dependency of 0.46 (95% CI 0.16 to 1.31), many observational studies of anticoagulation are available to support the use of anticoagulant which shows low mortality rates < 10%, likely due to underlying disease rather than CVST and majority of patients fully recovered neurological function, and few became disabled [13]. Data from observational studies suggest a range of risks for intracranial hemorrhage after anticoagulation for CVST from 0 to 5.4% [5,15,16]. Relatively, anticoagulant appear safe and effective. In a case of further neurological deterioration due to extensive thrombus despite of medical therapy, one can consider mechanical thrombectomy [13] and rarely surgical intervention is needed.

As of this case, two risk factors has been identified which are: Her underlying disease i.e SLE and initiation of OCP prior to onset of her neurological symptoms. It is quite challenging to differentiate the cause of CVST in this patient as her disease is active, thus cerebral lupus is on top of the diagnosis. As this is the second neurological presentation after initiation of OCP we conclude that her CVST is indeed induced by provera intake and not as part as her SLE manifestation.

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