

# Cerebral Venous Sinus Thrombosis induced By Hypercoagulation in Patient With Systemic Lupus Erythematosus: A Case Report and Literature Review

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**Introduction:** Systemic lupus erythematosus (SLE) are autoimmune diseases and cerebral venous sinus thrombosis (CVST) is coincidence regarding hypercoagulable condition of both diseases. The presence of both diseases in the same patient is rare, which suggests a relative incompatibility between these diseases.

**Case Presentation:** I report a female case with Systemic Lupus Erythematosus history, aged 27 years, with blurred vision, diplopia, severe headache, numbness and progressive right hemiparesis in 2 weeks. There was narrowing caliber at left transversus and right sigmoid sinus in magnetic resonance venography. She showed improvement in vision, numbness, headache and motor strength in right extremities after receiving pulse dose of corticosteroid for three days.

**Conclusion:** The distinction between SLE and CVST is a diagnostic challenge for the neurologist, and the presence of both diseases should be considered in patients with clinical neurologic manifestations who present with typical systemic manifestations of SLE and CVST. Neurogenic inflammation can induce disorders of the blood vessel wall (endothelium) that cause hypercoagulability and changes in acute vascular conditions can occur consisting of intraluminal platelet aggregation, thrombosis and also can cause total cerebral thrombotic venous or venular occlusion in SLE patients.

**Keywords:** cerebral venous sinus thrombosis, systemic lupus erythematosus, hypercoagulable state

## Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that is systemic in nature affecting the joints and several other organs including the skin, heart, lungs, kidneys and nervous system.<sup>1,2</sup> The involvement of the central, peripheral, and autonomic nervous systems and psychiatric disorders in SLE is termed 'neuropsychiatric lupus' (NPSLE).<sup>3,4</sup> Neuropsychiatric symptoms can also be one of the early manifestations of SLE. Research says that up to 40% of these symptoms appear during the first year after a diagnosis of SLE is made.<sup>5</sup> The most common manifestation of SLE with Central Nervous System (CNS) involvement is headache, followed by mood disturbances and cognitive dysfunction, stroke and seizures.<sup>5-8</sup>

I discuss a case report of SLE with Cerebral Venous Sinus Thrombosis (CVST) induced by hypercoagulable condition. Written informed consent to publish case details and any accompanying images was provided by the patient. Dr. Hasan Sadikin General Hospital Bandung Human Research Ethics Committee approved this consent process and institutional approval was required to publish the case details.

## Case Presentation

A 27-year-old female admitted to the emergency unit with blurred vision, diplopia, severe headache, numbness and progressive right hemiparesis in 2 weeks. She had history of Systemic Lupus Erythematosus (positive ANA profile) has

been recorded 5 years ago, and had routine medication before admission was mycophenolate sodium 360 mg every 8 hours and folic acid 5mg once daily.

## On Examination

Fully alert and normal vital sign. Low visus on both eyes (20/200) with positive Relative Afferent Pupillary Defect (RAPD) and right abducent cranial nerve palsy. Right facial and hypoglossal nerve palsy, hemiparesis and hemihypesthesia on right extremities.

## Laboratory Tests

WBCs  $9.69 \times 10^3/\mu\text{L}$ , RBC  $4.18 \times 10^3/\mu\text{L}$ , hemoglobin 10.60 (low) g/dL, platelet count  $333 \times 10^3/\mu\text{L}$ , neutrophils 94% (high), lymphocytes 5% (low), eosinophil 0%, basophil 5% and monocyte 1% (normal values: WBCs  $4\text{--}10 \times 10^3/\mu\text{L}$ , hemoglobin 12–15 g/dL, platelets count  $140\text{--}450 \times 10^3/\mu\text{L}$ , neutrophil 40–75%, lymphocytes 20–45%, monocytes 2–10%, eosinophils 2–6%, and basophils 0–1%). Prothrombin Time (PT) 13.30 seconds, aPTT 25.40 seconds, International Normalized Ratio (INR) 1.23 (high). D-dimer level 2.30 (high). Human Immunodeficiency Virus (HIV) antigen and Anti Phospholipid Antibodies was non-reactive. All electrolytes were in the normal limit. Liver and renal functions within the normal limit. Magnetic resonance venography showed narrowing caliber at left transversus and right sigmoid sinus (Figure 1). She was treated with intravenous methylprednisolone 500mg twice daily for three days, mycophenolate sodium 720 mg every 8 hours, warfarin 3 mg once daily, Mecobalamin 500mg every 8 hours, and Pregabalin 75mg twice daily for neuropathic pain symptoms.

After 7 days of hospitalization, she had improved the right limb's motor strength (walking with assistance), vision, headache, numbness and pain.

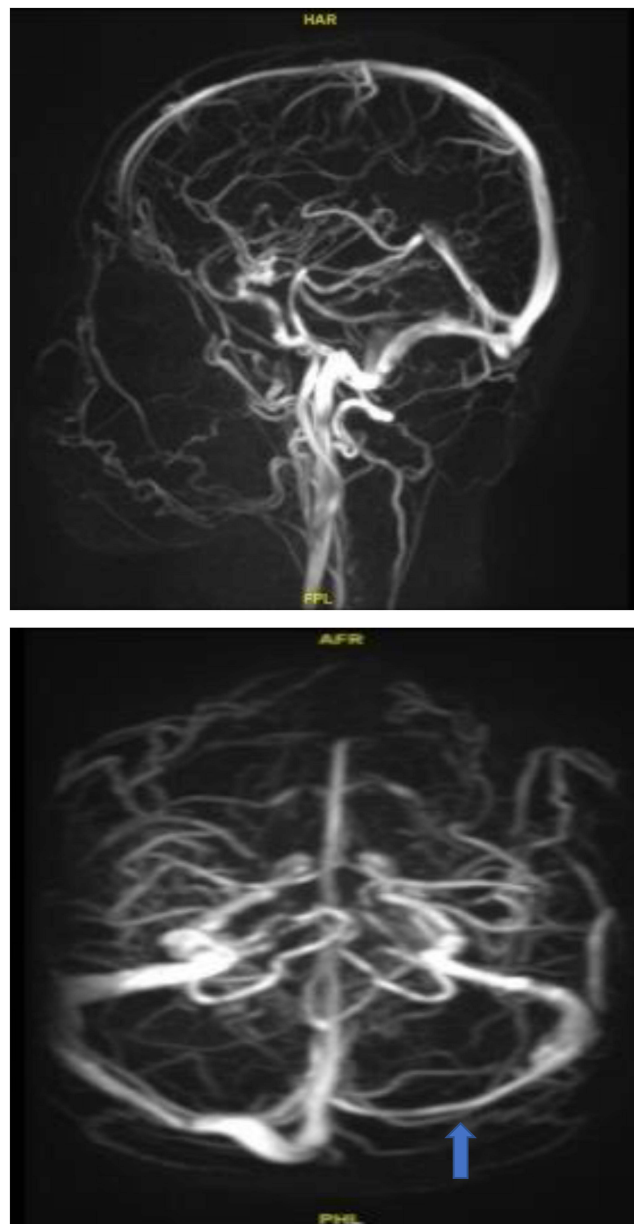
## Discussion

The most common manifestation of SLE with Central Nervous System (CNS) involvement is headache, followed by mood disturbances and cognitive dysfunction, stroke and seizures.<sup>4,5</sup>

### Headache Mechanism in SLE: Neuroinflammation and Hypercoagulability

The mechanism of the pathogenesis of headache in Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) is not completely clear, there are several possible causes. Many autoantibodies have been detected in plasma samples of SLE patients and have been associated with NPSLE. Some of them are anti-ribosomal-P, anti-DNA/NR2, anti-DNA (16–1 idiotypic), antiphospholipid (aPL), anticardiolipin (aCL) and Gamma Ammino Butyric Acid (GABA) antibodies.<sup>3,5,6</sup> It is hypothesized that auto-antibodies or pro-inflammatory cytokines circulating across the blood brain barrier (BBB) and entering the brain induce neurotoxicity.<sup>4</sup> Hawro et al reported that in NPSLE patients, the presence of autoantibodies was significantly associated with headache, ischemia, stroke and seizures.<sup>4,12</sup> The mechanisms that may be involved in the pathogenesis of the neuropsychiatric manifestations of SLE including headache in SLE patients are complex.<sup>12,14</sup> Several studies suggest that there are several factors such as genetics, vascular damage and occlusion, BBB dysfunction, nerve damage mediated by autoantibodies or inflammatory mediators including cytokines, and also direct neuronal cell death.<sup>4</sup> Two relevant pathogenetic pathways have been identified, namely the vascular-ischemic mechanism which is generally induced by aPL, immune complexes, and agglutination involving large and small blood vessels, which are considered to be more often responsible for the onset of focal neuropsychiatric symptoms.<sup>11,12,17</sup> The second is an inflammatory neurotoxic process whose mechanism is predominantly mediated by complement activation, increased BBB permeability, migrating intrathecal autoantibodies and local production of immune complexes and pro-inflammatory cytokines and other inflammatory mediators, which may lead to diffuse neuropsychiatric manifestations, consider the causes of infection, especially herpes virus infection which can occur as a result of SLE immunosuppression.<sup>3,5,6,9,10</sup>

Neuroinflammatory events involving activation of microglia and astrocytes also occur during the process of cortical spreading depression (CSD) which is the same pathophysiology of migraine with aura (MA).<sup>12,13</sup> Several preclinical studies have revealed that CSD not only induces glial cell activation but also increases the expression of pro-inflammatory cytokines, adhesion and chemokines as well as the expression of toll-like receptors (TLR3 and TLR4).



**Figure 1** Magnetic Resonance Venography of this patient. There was a reduction in the caliber of the left transverse sinus and the right sigmoid sinus (blue arrow).

Neurogenic inflammation involving the dural and wattle vessels and also can induce disorders of the blood vessel wall (endothelium) that cause hypercoagulability.<sup>31</sup> This causes several processes such as extravasation of plasma proteins due to increased meningeal vascular permeability and activation of immune cells, namely mast cells and macrophages.<sup>12–14</sup>

Mast cell activation will trigger the formation of several pain mediators such as serotonin, histamine, heparin, proteases and arachidonic acid products, pro-inflammatory cytokines and chemokines that are involved in trigeminal peripheral sensitization.<sup>15</sup> The C fibers of the trigeminal nerve will release calcitonin gene-related peptide (CGRP) which interacts with its own receptor on the dural vessels. This interaction will activate adenylate cyclase which causes dilation of blood vessels so that it will trigger pain.<sup>16</sup> Astrocytes and glial cells also have CGRP receptors. The interaction of CGRP with its receptors on astrocytes and glia cells will induce the release of several pro-inflammatory cytokines such as tumor necrosis factor (TNF)- $\alpha$  and interleukin (IL)-1 $\beta$  which dramatically amplify trigeminal nociception.<sup>16–18</sup>

There is controversy over the pathogenesis of SLE and CVST involving autoimmunity.<sup>15</sup> Several immunological mechanisms lead to inflammation of the blood vessel walls and an increase in the permeability of the blood-brain barrier.

In addition, perivascular leukocyte accumulation is associated with increased serum protein deposition. In addition, in some cases, changes in acute vascular conditions can occur consisting of intraluminal platelet aggregation and thrombosis and can cause total thrombotic venous or venular occlusion. In some cases, a severe inflammatory reaction has been observed in association with the veins.<sup>18,25</sup> Impaired blood flow due to blockage of the venous system will cause increased pressure on brain tissue, because the venous system is blocked in the dural sinus area. Increased pressure on brain tissue will cause brain edema around the blockage area of the venous system. Furthermore, the capillaries and arterioles will rupture and cause cerebral hemorrhage, if the pressure increases higher, the bleeding can spread to the nearest subarachnoid space causing decreased consciousness to death.<sup>31</sup>

In this patient there is thrombosis in the vein (CVST) which can be caused by hypercoagulable conditions (elevated of D dimer level) and will cause blockage of venous system resulting in increased intracranial pressure (benign intracranial hypertension). The complex interaction between endothelial cells and Lupus Antibody (LA) will trigger inhibition of proteins C and S that can cause hypercoagulable state which are responsible for the occurrence of thrombosis.<sup>25</sup> Impaired fibrinolysis, antithrombin III, hyperfibrinemia, or changes in coagulation may also lead to thrombosis.<sup>14,15,25</sup>

The presence of optic neuropathy and MRI images in the form of ovoid lesions with hyperintense T2 in the parietal and occipital subcortical areas accompanied by bilateral optic neuritis images suggest a demyelination process (multiple sclerosis) which is still possible to diagnose in comparison with SLE lesions.<sup>19,20</sup> In addition, optic neuropathy in SLE can also be caused by an ischemic process. Fluorescein angiography can help differentiate between some cases of optic neuritis and ischemic optic neuropathy, which often results from thrombosis or vasculitis.<sup>9,12</sup> It is also important to consider the cause of infection, particularly herpes virus infection, which can occur as a result of SLE immunosuppression.<sup>17,18</sup>

## Management of SLE with CVST

Adrenocorticotrophic (ACTH) hormone gel was approved by the United States Food and Drug Administration as a treatment option for SLE in 1952.<sup>23,24,29,30</sup> ACTH has anti-inflammatory and immunomodulatory effects due to activation of central and peripheral melanocortin receptors.<sup>30</sup> Regarding SLE patients with moderate or severe active SLE, an open-label study showed that ACTH gel may provide significant disease activity reduction.<sup>29,30</sup>

However, there is controversy regarding the administration of high-dose steroids in CVST patients. The use of steroids is associated with coagulation status so that it can affect the CVST condition. Patients with chronic inflammatory disease are at risk for venous thromboembolism (VTE).<sup>25</sup> The risk of developing VTE is related to an exacerbation of the disease usually treated with corticosteroids.<sup>26</sup> When corticosteroids induce a procoagulant state, patients with exacerbations and receiving corticosteroid therapy have a very high risk of developing VTE. Hypercoagulability induced by steroid therapy is associated with elevated factors VII, VIII, and XI. There are studies that show an increase in FVIII levels after short-term administration of high-dose dexamethasone in healthy men, which is in line with observations in patients with Cushing's syndrome. However, other non-genomic studies have shown that high doses of acute glucocorticoids increase activation of endothelial nitric oxide synthase (eNOS), which may inhibit VWF secretion. While endothelial dysfunction and increased oxidative stress and chronic insulin resistance associated with excess glucocorticoid in the long term have been reported to increase plasma VWF levels. It is also explained that the long-term use of oral corticosteroids allows for an increase in factors II, V, VII, IX, X, XII and fibrinogen which further induces a hypercoagulable state.<sup>21,22,25,26</sup>

In addition, the presence of steroid therapy in SLE can interact with anticoagulant therapy, namely warfarin which is used as CVST therapy.<sup>22</sup> There are studies showing a supratherapeutic effect of INR in individuals taking warfarin and steroids. The exact mechanism of interaction between warfarin and oral corticosteroids is not clearly known, but it is thought to be related to the process of both drugs in the liver. Methylprednisolone, prednisone, and warfarin are metabolized in the liver via the CYP3A4 isoenzyme pathway.<sup>26</sup> Inhibition of warfarin metabolism potentially occurs as a result of competitive binding to CYP3A4. In addition to the CYP3A4 pathway, warfarin is also a substrate for the CYP1A2, 2D6, and 2C9 isoenzyme pathways. However, there is another influence, namely genetic deficiency of the cytochrome P450 isoenzyme that causes various compensatory warfarin metabolism through different isoenzyme pathways. Kaufman says another possible theory of warfarin's effect with steroids is related to serum pH. The use of steroids

will increase the serum pH which can cause the binding of warfarin to protein to decrease so that it will increase the free warfarin level in the blood.<sup>26,27</sup>

In this patient was treated with intravenous methylprednisolone 500mg twice daily for three days, mycophenolate sodium 720 mg every 8 hours, warfarin 3 mg once daily, Mecobalamin 500mg every 8 hours, and Pregabalin 75mg twice daily for neuropathic pain symptoms. After 7 days of hospitalization, she had improved the right limb's motor strength (walking with assistance), vision, headache, numbness and pain. It needs to be watched out for in relation to the possibility of bleeding side effects from warfarin use.<sup>25,26</sup>

## Limitation of Study

This article had several limitations. I did not assess the panel of pro-inflammatory assay in this patient.

## Conclusion

The distinction between SLE and cerebral venous sinus thrombosis is a diagnostic challenge for the neurologist, and the presence of both diseases should be considered in patients with clinical neurologic manifestations of SLE who present with headache and neurological deficit. Neurogenic inflammation can induce disorders of the blood vessel wall (endothelium) that cause hypercoagulability and changes in acute vascular conditions can occur consisting of intraluminal platelet aggregation, thrombosis and also can cause total thrombotic venous or venular occlusion in cerebral of SLE patients. Health-care professionals, involved clinicians, especially neurologist, should be informed to with this complication, addressing a prompt diagnosis and proper treatment to decrease the CVST-related morbidity and public health burden in SLE patients.

## Disclosure

The author reports no conflicts of interest in this work.

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