



# Neurological complications as the hallmark symptoms of thrombotic thrombocytopenic purpura in sickle cell disease

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## Key point

Thrombotic thrombocytopenic purpura (TTP) is a type of microangiopathy, which is characterized by the formation of small blood clots in the vessels, leading to organ damage and low platelet count. In sickle cell disease (SCD), TTP can occur due to the activation of the coagulation system and damage to the endothelial cells lining the blood vessels. The importance of TTP in SCD lies in its potential to cause severe and life-threatening complications, including stroke, renal and heart failure. Early recognition and treatment of TTP in SCD are crucial to prevent these complications and improve outcomes. In this letter, we highlighted the significance of neurological complications in the diagnosis of TTP in SCD.

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## Introduction

Sickle cell disease (SCD) is an inherited abnormality of the beta-hemoglobin chain that leads to hemolytic anemia. The molecular basis of this disease is a mutation on the beta-globulin gene on chromosome 11 that leads to S hemoglobin formation. In homozygous individuals, S hemoglobin are translated and can polymerize to form long fibers. These fibers change the morphology of erythrocytes into a sickle form. The sickle erythrocytes interfere with blood flow in small vessels and can induce hypoxia, inflammation, and other complications depending on the site of involvement (1).

Frequent sickling is associated with increased endothelial adhesion molecules such as selectins, intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1). Adhesion of circulating blood cells results in the upregulation of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-1 (IL-1), IL-2, and IL-8. On the other hand, chronic hemolysis in SCD

patients elevates the free hemoglobin level. Free hemoglobin acts as a nitric oxide (NO) scavenger and diminishes its blood level. Thus, the anti-inflammatory and vasoactive roles of NO are diminished. In this process, the iron release also triggers the production of free oxygen and nitrogen species. This condition contributes to chronic inflammation, leading to more damage to the endothelium. All of these pathways result in vasoconstriction, vaso-occlusion, systematic thrombosis, and hypercoagulation (2).

SCD-related central nervous system complications have been the focus of studies on SCD in the last 40 years. Silent cerebral infarcts, stroke, and myopathy comprise most of these complications. Stroke is the most prevalent neurological complication of SCD and mainly manifests with hemiparesis, hemisensory loss, and aphasia. Six risk factors are suggested to be associated with ischemic events in SCD patients:

1. Hypoxia
2. Cerebral vasculopathy
3. Acute fever due to infections

4. Underlying cardiovascular diseases
5. Having a history of cerebral infarction in the past three years
6. Rapid hemoglobin level increase to above 12 g/dL (3).

The expanded endothelial adhesion, coupled with expanded shear stress due to anemia, may provoke the injury of endothelial cells of the blood vessels, including the cerebral arteries. This condition leads to other processes, including oxidative injury of the vessel wall, inflammation, abnormal vasomotor regulation, and increased coagulation. The SCD-associated anemia results in hyperemia and vasodilation throughout the body, resulting in increased cerebral blood flow and further perfusion to the brain during hypoxic stress. A key contributor to vaso-occlusion may be the increased tendency of the sickle cells to stick to the vascular endothelium. When sickle cells attach to the vascular endothelium, capillary transit time increases. The precipitating factors of the sickling phenomenon include hypoxia, dehydration, and metabolic acidosis. Hence, in several severe consequences of SCD, acute stroke and chronic cerebral ischemia are among the most disabling vascular anomalies besides neurocognitive impairment (4).

Thrombotic thrombocytopenic purpura (TTP) is a microangiopathic hemolytic anemia caused by dysfunction of the enzyme ADAMS13. ADAMS13 is a metalloprotease that cleaves von Willebrand factor (VWF) into high, intermediate, and low weight molecules. The dysfunction of ADAMS13 can be related to autoimmune diseases, genetic conditions including SCD, viral infections, some solid organ and hematological cancer, pregnancy, and medication use. This disease leads to thrombus forming in small blood vessels, kidneys, heart, and brain damage. Traditionally, TTP is diagnosed by observation of five concomitant signs and symptoms, including fever, microangiopathic anemia, renal dysfunction, mental status deterioration, and thrombocytopenia (5). However, neurological complications are the most common symptoms. These complications include headache, confusion, ataxia, seizures, mental status deterioration, and focal abnormalities, which present in up to 60% of TTP episodes. Although the central nervous system is the main target organ of TTP, the risk factor associated with neurological complications are not established yet (6). Thrombotic thrombocytopenic purpura and SCD can occur concomitantly. This is a rare yet life-threatening condition. TTP has a distinct etiology in SCD patients. In SCD patients, endothelial adhesion molecules-mediated inflammation prevents ADAMS13 from cleaving the von Willebrand factor via two mechanisms;

1. Suppression of the ADAMS13 expression by megakaryocytes and endothelial cells
2. Recruitment and adhesion of glycoprotein Iba and leukocytes to the VWF thwarts ADAMS13 from accessing its binding sites (7).

The similarity of the symptoms of these two diseases makes a differential diagnosis problematic. The current treatment protocol for this condition suggests waiting for a full-blown set of TTP symptoms. Nevertheless, TTP requires prompt treatment and any hesitation significantly decreases the patient's life expectancy (8). In our clinical experience, of all of the five typical symptoms of TTP, mental status deterioration, in harmony with a high serum LDH level (>600 IU/L) is the first indicator of TTP in SCD patients. In most cases, the other classic indicators of TTP, including fever, microangiopathic anemia, kidney dysfunction, and thrombocytopenia are not necessary for the differential diagnosis. Since CNS is the target organ in both diseases through the mentioned mechanisms, we believe that neurological complications are the most important symptoms of TTP in SCD. It is crucial to review the confirmatory criteria of TTP diagnosis in SCD and conduct more studies on the significance of neurological symptoms to increase the survival rate of patients with this condition.

#### Authors' contribution

Conceptualization: MB, BK, EA.  
Validation: BK, SR, RM.  
Investigation: MB, EA.  
Writing—Original Draft Preparation: EA.  
Writing—Review And Editing: MB, EA and NNGF.  
Supervision: BK, SR, RM.  
Project administration: RM.

#### Conflicts of interest

The authors declare that they have no competing interests.

#### Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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