Diagnosis of Scott syndrome in patient with bleeding disorder of unknown cause

Scott syndrome is a rare bleeding disorder due to an impaired exposure of phosphatidylserine on the platelet membrane, compromising the platelet procoagulant activity, thrombin generation and, thus, the clot formation. We report a case of a 17-year-old female adolescent with bleeding episodes of unknown cause. She had normal coagulation, but altered platelet aggregation under arteriolar flow, indicating platelet dysfunction. Furthermore, the expression of Annexin V was markedly reduced and the diagnosis of Scott syndrome was established. She was treated with platelet transfusions and demonstrated a clinical improvement. Scott syndrome may be investigated in cases with bleeding history and normal coagulation tests. Blood Coagul Fibrinolysis 2012, 23:75–77

Introduction
Scott Syndrome is a rare bleeding disorder caused by a less-active phosphatidylserine transporter. Because of this, the phosphatidylserine remains sequestered in the inner leaflet of the platelets, compromising the formation of the tenase and prothrombinase complexes and impairing the thrombin generation, resulting in hemorrhagic complications [1–3]. As this disease is not detectable by standard coagulation tests, further coagulation assays may be necessary for the orientation of diagnosis and laboratory monitoring of the treatment [4].

We report the case of a 17-year-old female adolescent with a bleeding disorder of unknown cause, who presented normal specific coagulation tests, but altered platelet aggregation under shear stress.

Case report
A 17-year-old white female adolescent was referred to the Emergency Department of the State University of Campinas in June 2009 to investigate abdominal pain, accompanied by episodes of hematemesis. She also reported other bleeding episodes, such as gingival bleeding, epistaxis, intestinal bleeding due to ulcer, hemorrhoid and hemorrhagic events after three surgeries, which were treated with blood transfusions. During the hospitalization period, she deteriorated clinically, presenting hematuria, hemoptysis, metrorrhagia and severe anemia. The results of the gastrointestinal upper tract endoscopy, pelvic and abdominal ultrasound and chest radiograph were normal and excluded local causes of the bleedings.

Upon hospitalization, the patient presented normal blood counts, despite a mild anemia and normal coagulogram parameters. During the diagnostic investigation, the bleeding time and the plasma levels of the factors V, VII, VIII, XI, XIII and von Willebrand factor were normal. Inhibitors of coagulation factors were negative and the plasma levels of fibrinogen were discretely increased (491.1 mg/dl). The platelet aggregation test, applying the agonists 5 μmol/l ADP, 5 μmol/l adrenaline, 2 mg/ml collagen, 0.5 mmol/l arachidonic acid and
ristocetine (0.6 and 1.25 mg/ml), was also normal. The expression of the platelet surface glycoproteins, GPIb-IX and GPIIb-IIIa was determined by flow cytometry using CD42a, CD42b, CD41 and CD61 monoclonal antibodies and were also normal.

High shear stress platelet aggregation [the Impact: Cone and Plate(let) Analyzer (CPA) Technology] [5] showed decreased platelet aggregate sizes (average size 21 μm²) and a decreased surface covered by aggregates (area covered 6.6%) in comparison with a healthy individual (Fig. 1a and b; average size 73 μm², area covered 11%). This assay confirmed the hypotheses of platelet dysfunction.

The phosphatidylserine exposure on the platelet membrane was then studied by flow cytometry, with thrombin stimulation [6]. Platelet-rich plasma was incubated with

![Diagram of platelet aggregation](image)

The phospholipid exposition was analyzed in platelets from healthy individuals (upper plots) and from the patient (lower plot). The platelets were labeled with Annexin V and CD61 without any stimulation (panels a and c) or after incubation with 0.1 U/ml of thrombin with CaCl₂ 2.5 mmol/l (panels b and d). On healthy controls, the mean percentage increased from 7.05% before stimulation to 12.27% after stimulation (panel b), whereas the patient’s percentage decreased from 6.07% (panel c) to 3.72% (panel d) in the same conditions.
Annexin V-FITC (25 µg/l) for a specific binding to phosphatidylserine and CD61-PE (0.125 g/l) for platelets. The phosphatidylserine membrane expression was two to four times lower on patients’ platelets (2.55%) when compared with four healthy controls’ platelets (Fig. 2): 12.43% (control 1), 7.72% (control 2), 7.12% (control 3) and 6.47% (control 4).

These results suggest a diagnosis of Scott syndrome. The patient was treated with platelet transfusion, demonstrated an improved clinical outcome and was discharged from hospital 5 days after the beginning of therapy.

**Discussion**

In the case reported, we present a challenging diagnosis of Scott syndrome. In recent years, there has been a recognition that specific assays of coagulation may not be sufficient to assess the patient’s overall haemostatic state, and that more global tests may offer additional information [7]. There is no evidence, however, of which assay should be the standard to evaluate patients with bleeding disorders of unknown cause.

Scott syndrome may be suspected in cases of moderate or severe hemorrhagic disorders associated with normal coagulation tests. Zwaal et al. [3] mentioned that platelet count and structure are usually normal, and no aberrations of platelet secretion, aggregation, metabolism, granule content or platelet adhesion to subendothelius have been detected in Scott syndrome carriers.

In the present case, despite the clinical presentation of severe bleeding episodes, all specific tests of coagulation performed gave normal results and only the CPA assay, which evaluates the global function of platelets, raised the possibility of a platelet dysfunction. Recently, this system has been considered a very useful tool for testing platelet function (adhesion and aggregation) under physiological arteriolar flow conditions. This test has been useful for the prediction of bleeding in cardiac surgery patients [8], for the diagnosis of afibrinogenemia, von Willebrand type III, Bernard–Soulier syndrome [9], Glanzmann thrombasthenia and for thrombotic microangiopathies, such as thrombotic thrombocytopenic purpura [10]. The CPA assay, in this case, was essential for the diagnosis of platelet dysfunction, and the flow cytometry confirmed the diagnosis, as previously described, of Scott syndrome [6].

Although this is a rare disease, it is important to rule out Scott syndrome in cases of moderate or severe hemorrhagic disorders, associated with normal coagulation tests, in the absence of other compelling explanations. Furthermore, global tests and functional assays of coagulation are required to address the diagnosis of uncommon coagulopathies, frequently diagnosed as bleeding disorders of unknown cause. In this field, CPA assays may play an important role in the diagnosis of platelets disorders.

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**Conflicts of interest**

There are no conflicts of interest.

**References**