Original Article

Immune-Thrombotic Thrombocytopenic Purpura is a Rare Cause of Ischemic Stroke in Young Adults: Case Reports and Literature Review

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Introduction: Immune thrombotic thrombocytopenic purpura (i-TTP), related to acquired ADAMTS-13 dysfunction, can lead to various neurological symptoms including ischemic stroke. To date the clinical, radiological, and biological characteristics of patients having a stroke as the inaugural manifestation of i-TTP are largely unknown. *Methods:* Probable immune-TTP was defined by a low ADAMTS-13 activity associated with the presence of ADAMTS-13 inhibitors and/or favorable clinicobiological response under immunological treatments. The clinical, radiological, biological data and outcome under treatment are described in a cohort of 17 patients coming from 3 local cases and a literature review. *Results:* Fourteen of the 17 patients were female and the mean age was 41 years. None of the patients had the classical pentad of TTP. Only 41% had a combination of thrombocythemia and hemolysis. Stroke was multifocal in 35% and included large artery strokes. No adverse event was observed following intravenous thrombolysis. Refractory and relapsing forms were observed in 47%. *Discussion:* The clinical, radiological, and biological presentation of patients with stroke as the inaugural presentation of i-TTP is heterogeneous. This diagnosis should be discussed in every young adult with ischemic stroke of undetermined source.

Key Words: Ischemic stroke—thrombotic micro angiopathy—immune thrombotic thrombocytopenic purpura

Introduction

About 35% of ischemic strokes (IS) are of undetermined source after first-line investigations.[1] This rate includes a large number of rare diseases, including coagulation disorders that account for less than 5% of stroke mechanisms.[2] Thrombotic thrombocytopenic purpura (TTP), which is a consequence of an inherited or acquired ADAMTS-13 dysfunction, is part of the thrombotic microangiopathy (TMA) syndromes.[3] TTP has been historically associated with a pentad associating thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fever, neurological symptoms, and renal insufficiency. However, this full spectrum is observed in less than 10% of the patients.[4] Herein we report 3 cases of IS associated to probable immune-TTP and make a literature review of the clinical and biological characteristics reported in patients having an IS as the inaugural clinical presentation of this rare disorder. ADAMTS-13 inhibitor

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was determined using a neutralizing inhibitor approach as previously described[5] and anti-ADAMTS-13 IgG was determined by Enzyme Linked ImmunoSorbent Assay (ELISA) (TECHNOZYME ADAMTS-13 INH, Technoclone, Austria). Our laboratory cut-off for a positive value was >35 IU/mL.

Cases Reports

Case 1

A 33-year-old patient was admitted for a sudden binocular diplopia, related to a left oculomotor nerve palsy, and right ataxia (National Institute of Health Stroke Score [NIHSS] = 2). General examination was normal with no fever. He was an occasional smoker, and had a pertussis vaccination 1 month before. Admission MRI (Fig 1, A,B) showed a right punctiform cerebellar infarct on diffusion-weighted sequences. CT-angiography of the supra-aortic vessels was normal. Intravenous thrombolysis was started and stopped early after initiation because of a platelet count of 80 g/L (80000/mm^3). Serum biological analysis did not demonstrate other cytopenia, or disseminated intravascular coagulation (fibrinogen, fibrin degradation product, and prothrombin time levels were normal). No abnormality of the hemolysis biomarkers was initially observed. C-Reactive Protein (CRP) level was normal. Troponin level was normal and there was no liver insufficiency. No renal insufficiency was found (creatinine clearance 167 mL/min), but an increased proteinuria/creatininuria ratio (129 mg/mmol; normal (N) < 15) was observed. Neither antiphospholipid antibodies nor lupus anticoagulant was found. Autoimmune parameters (complement level, immunoglobulin quantitation, anti-DNA and extractible nuclear antigens (ENA) antibodies) were normal except for a nonsignificant increase of dense fine speckled antinuclear antibodies (1/320). Myelogram suggested a peripheral thrombocytopenia. A low ADAMTS-13 activity (below 5%) together with the presence of anti-ADAMTS-13 antibody was found at day 5, leading to the diagnosis of immune-TTP. Evolution of the main biological abnormalities from admission to discharge is summarized in Table 1. Oral corticotherapy (1 mg/kg) combined to plasma exchange (PE) was

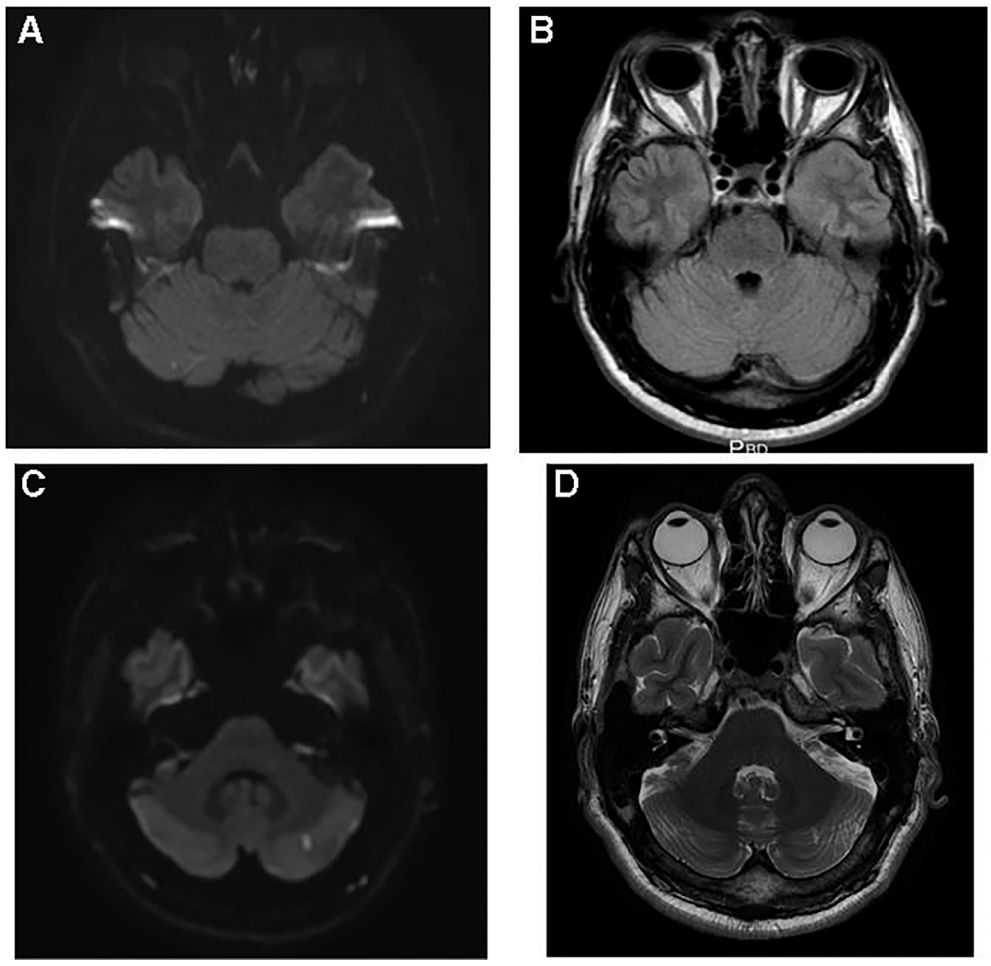

Figure 1. *MRI images of patient 1. (A) Day 1 before alteplase; Diffusion sequence; (B) Day 1 before alteplase; Flair sequence. (C) Control; diffusion sequence; (D) Control; T2 sequence.*