



Recurrent and Refractory Ischemic Stroke Complicating Evans Syndrome

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Abstract

Evans Syndrome (ES) is characterized by autoimmune hemolytic anemia and immune thrombocytopenia. ES rarely manifests thromboembolic events of the Central Nervous System (CNS), especially cerebral infarction. We experienced a 72-year-old woman with ES accompanied by recurrent and refractory cerebral infarction. Laboratory studies showed anemia with positive Coombs test and thrombocytopenia. Lupus and other rheumatologic studies were normal. Magnetic Resonance Imaging (MRI) of the brain depicted acute cerebral infarction in the right MCA territory. Abnormal laboratory profiles normalized with the administration of prednisone. However, cerebral infarction recurred twice in both MCA territory despite the stabilization of ES. Transthoracic and trans-esophageal echocardiography showed no abnormality. Hypercoagulability, which is one of the most precipitating factors of stroke, may attribute to the pathomechanism of the cerebral infarction in Evans's syndrome.

Keywords: Evans syndrome; Autoimmune hemolytic anemia; Recurrent cerebral infarction; stroke

Introduction

Evans Syndrome (ES), which was first described in 1951, is an autoimmune disorder characterized by the simultaneous or sequential development of Autoimmune Hemolytic Anemia (AIHA) and Immune Thrombocytopenia (ITP), and/or immune neutropenia in the absence of any underlying cause [1,2]. The association between cerebral infarction and ES is infrequent, and only a few venous thrombosis cases have been reported [3-5]. Herein, we report a patient with recurrent ischemic stroke complicating ES, refractory to antithrombotic treatment.

Case Presentation

A 72-year-old woman presented with left upper extremity weakness, begun three days ago. On the neurological examination, she had dysarthria and her motor weakness was predominant in the left proximal upper extremity (MRC grade II) with hyperactive deep tendon reflexes. Cortical sensory and somatosensory examinations were relatively normal. Vital signs were stable, and there were a few ecchymoses on her extremities. She had antihypertensive medication and had been treated with right femoral vein thrombosis three years before. She had severe anemia (hemoglobin 7.4 g/dL) requiring transfusion with a lower normal limit of the platelet at that time. However, she had not undergone further hematologic evaluations for the anemia. Then, she maintained anticoagulation therapy for six months that was stopped by herself. Laboratory abnormalities on admission showed as follow: Hemoglobin 10.7 g/dL, MCV 87.2 fL, corrected reticulocytes 2.2%, WBCs 16.1 ($\times 10^9/L$), platelets 34 ($\times 10^9/L$), AST 26 IU/L, total bilirubin 0.42 mg/dL, LDH 712 IU/L. A subsequent direct/indirect Coombs tests were positive. She had a decreased renal function (<45 mL/min). The result of antiphospholipid antibodies and other rheumatologic studies, including FANA and anti-dsDNA antibody was negative. We started pulse therapy with methylprednisolone (1000 mg/day for 3 days) followed by oral prednisolone (60 mg/day) under idiopathic Evans syndrome diagnosis. Brain MRI with Diffusion-Weighted Imaging (DWI) depicted multiple high signal intensities in the right pre- and postcentral gyri (Figure A). There was no stenosis or occlusion of intra- and extracranial vessels (Figures B and C). Cardiac evaluation with electrocardiography and transthoracic echocardiography was normal. Thrombocytopenia was persisted under 50 ($\times 10^9/L$), and we deferred the treatment of stroke with an antiplatelet agent. She was discharged with maintaining a high dose of prednisolone (60 mg). Anemia and thrombocytopenia came to normal within two months. We started 100 mg of aspirin and blood cell counts kept stationary with 10 mg of prednisolone. Three months after the first attack, the patient re-admitted, complaining of dizziness and gait disturbance. Left

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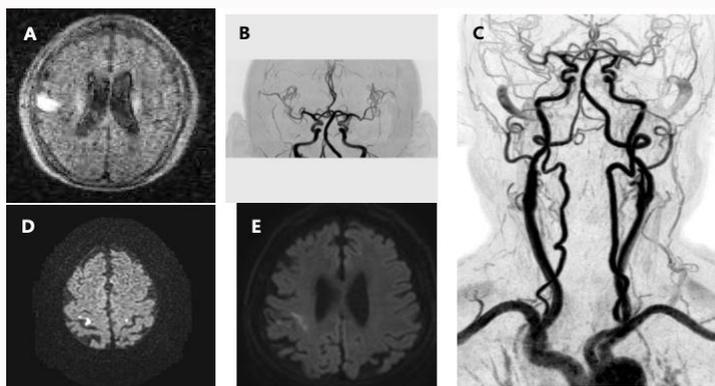


Figure 1: Serial diffusion-weighted images (A: First, D: Second, E: Third admission). No definite occlusion, intra- and extracranial arteries (B, C) at first admission.

upper extremity weakness was improving status but persisted (MRC grade IV). Laboratory tests were stable except for renal impairment. DWI of the brain showed new multifocal ischemic lesions around the left precentral gyrus (Figure D). Further cardiac studies, EKG Holter monitoring and trans-esophageal echocardiography, showed no abnormality besides mild decreased ejection fraction (49%). Coronary angiography was normal. We replaced aspirin with anticoagulation therapy. No neurologic impairments remained at the time of discharge. Seven months after the second stroke, the patient was re-admitted complaint of left leg weakness. On examination, pronator drift was in the left arm and mild ipsilateral weakness (MRC grade IV) in the leg. There were new lesions of the right precentral gyrus in the follow-up MRI (Figure E). Just like the second attack, blood cell counts were stationary. We added cilostazol (200 mg/day) to the warfarin. Three days later, motor weakness normalized, and the patient was discharged with the combination therapy.

Discussion

Evans Syndrome (ES) is a rare condition because it is diagnosed in only 0.8% to 3.7% of all patients with either ITP or AIHA at the onset [6]. Few and mainly pediatric data on ES are available in the literature [7-9]. Therefore, the characteristics and outcome of adult's ES are poorly known [10]. As the presence of AIHA and ITP, hemorrhagic or thromboembolic events can be a natural manifestation of ES. In particular, the influence of cerebrovascular hemorrhage could be life-threatening or nonfatal [11]. Despite the increased risk of thrombosis in ES patients [12], the relationship between ES and ischemic stroke is not clear yet and rarely reported in literature [4,13]. There have been only a few reports in case of thrombotic complication regarding cerebral venous thrombosis in ES [3,5]. In this case, ES was diagnosed because the patient tested positive for hemolytic anemia by the Coombs test, and for idiopathic thrombocytopenic purpura, in the absence of any known underlying etiology. It is doubtful that the severe anemia found three years ago was AIHA. Looking at the natural course of the patient, ES was reactive to the high dose of prednisolone. Even during the stable state of ES, cerebral infarction recurred despite using an antiplatelet or anticoagulation agent. The pathomechanism of thromboembolic events in ES remains unknown in most reports. Hypercoagulable state is proposed as a main mechanism of this manifestation. A hypercoagulable state seems to occur in the recovery period from hemolytic anemia and thrombocytopenia, in some way resulting from the therapeutic acceleration of hematopoiesis [5]. Another explanation suggests products of hemolysis could have impact on vasulotoxicity and coagulation system resulting

subsequent thromboembolic events [14]. The influence of long-term use of prednisolone could have partial effect on hypercoagulability. However, as the contradictory result whether the corticosteroid affect hypercoagulability of the blood [15,16], the effect of prednisolone on the thrombotic manifestation could be controversial. There had been no reports that cerebral infarction was presenting diagnosis of ES and recurrence of cerebral infarction. We could not find any other cause of stroke besides hypertension, one of the risk factors of ischemic or hemorrhagic stroke. It is known that a significant number of patients with cerebral thromboembolism have one or more predisposing conditions for thrombosis [17]. The risk of cardiovascular complications like acute coronary syndrome or stroke could be also increased related to AIHA especially in elderly ES patients [10]. This implies the risk of thrombotic event outweighs the risk of bleeding events in elderlies. Moreover, in periatric patients, even though no known risk factor for ischemic stroke, ES accompanied with stroke. There is no standard treatment of cerebral infarction in patients with ES until now. In summary, it is noteworthy that ES complicates ischemic stroke at the initial state. It may be the first case in the thromboembolic manifestation of ES, which was a presenting event, and recurrence of ischemic stroke in ES might be very rare. We prescribed an antiplatelet agent and combination with anticoagulation for recurrence. We think ischemic stroke can occur in any stage of ES. The medical treatment for ischemic stroke in patients with ES should be studied further to improve comorbidity outcomes.

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