신생아기에 발병한 출혈성 뇌경색증 및 심실내 혈전증을 동반한 선천항트롬빈결핍증 1예

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Hereditary Antithrombin Deficiency with Hemorrhagic Cerebral Infarction and Cardiac Thrombosis Occurred in Neonatal Period: A Case Report

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Antithrombin (AT) is the main inhibitor of blood coagulation proteases. Hereditary AT deficiency is an autosomal-dominant thrombophilic disorder caused by a SERPINC1 abnormality, it represents a risk factor for thromboembolic disease. A 25-day-old male infant was referred to Severance Children's Hospital for hemorrhagic cerebral infarction with hydrocephalus. The initial laboratory study showed 11% AT activity. An approximate 4 mm-×-3 mm-size thrombosis was also found in the right ventricle by echocardiography. We found two deletion in the coding and flanking sequences of SERPINC1 c.235C>T (p.Arg79Cys) and c.442T>C (p.Ser148Pro) at 10 months of age. The p.Ser148Pro mutation was found in his mother but the other was not. This case is a rare thrombotic event that occured early year in due to AT deficiency. Our patient had side effects after heparin treatment, so aspirin therapy was employed. No thrombotic events occurred until 1 year of age.

Key Words: Antithrombin deficiency, SERPINC1, Neonatal cardiac thrombosis

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Introduction

Antithrombin (AT) is a plasma serine protease inhibitor (serpin) that inactivates a number of proteases in the coagulation cascade, particularly thrombin and factor Xa [1]. Inherited AT deficiency is divided into type I deficiency, in which both the functional activity and antigenic levels of AT are proportionately reduced (quantitative deficiency), and type II deficiency, in which normal antigen levels are found in association with low AT activity due to a dysfunctional protein [2]. Type I AT deficiency, caused by an abnormality in the AT gene [serpin peptidase inhibitor clade C member 1 (SERPINC1)], is inherited as an autosomal-dominant disorder associated with a predisposition to recurrent venous thromboembolism (TE) [3]. Currently, extensive gene analyses of inpatients with AT deficiency have revealed many distinct SERPINC1 defects, including missense, nonsense, deletion, and insertion mutations [4]. Prevalence rates for AT deficiency of 1 in 500 to 1 in 5,000 in the over-

all population have been reported [5].

Thrombosis is suspected to be hereditary when a thrombotic event occurs at a relatively young age, when there is a family history of thrombotic disease, and when there is a recurrence of thrombotic events [6]. Patients with AT deficiency are at a significantly increased risk for TE, but the risk increases significantly around the age of 20 years [3].

We identified a case of hereditary AT deficiency with hemorrhagic cerebral infarction and cardiac thrombosis during the neonatal period.

Case Report

The patient was born by cesarean section due to preeclampsia of the mother at 37+1 weeks with a birth weight of 2.03 kg; the patient was admitted to the neonatal intensive care unit for respiratory difficulty, disseminated intravascular coagulation, and brain hemorrhage. The patient was referred to Severance Children's Hospital at 25 days for surgical management of hemorrhagic cerebral infarction with hydrocephalus. We could not identify the exact time of brain hemorrhage, but we suspected that the infarct hemorrhage occurred during the antenatal period because hemorrhages and hydrocephalus were found by brain computed tomography imaging on the day of birth (Fig. 1).

A brain magnetic resonance imaging study was done at 42 days of age; we found a large bilateral subdural hemorrhage, a subacute intracranial hemorrhage in the right parietal lobe, and suspected thrombi in the straight and bilateral transverse sinuses (Fig. 2). An approximate 4×3 mm size thrombosis was found in the right ventricle as a round echogenic mass by echocardiography (Fig. 3). An initial laboratory study found only 11% of AT activity. White blood cell count was $8,880\times10^3/\mu L$, hemoglobin was 10.5 g/dL, and platelet count was $169\times10^3/\mu L$. Prothrombin time was 8.6 seconds, and activated partial prothrombin time was 27.0 seconds. D-dimer levels were elevated at 17,958 ng/mL, and fibrinogen levels were 284 mg/dL.

We could not determine the actual cause of thrombosis at birth and chose heparin for anticoagulation treatment. This therapy was terminated due to thrombocytopenia,

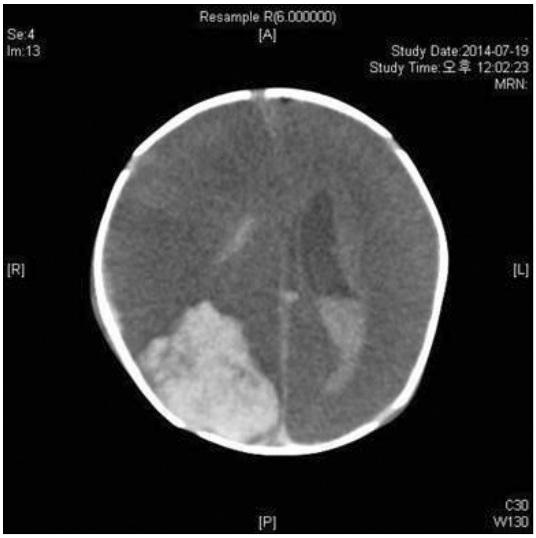

Fig. 1. Hemorrhages and hydrocephalus were found by brain computed tomography imaging on the day of birth.

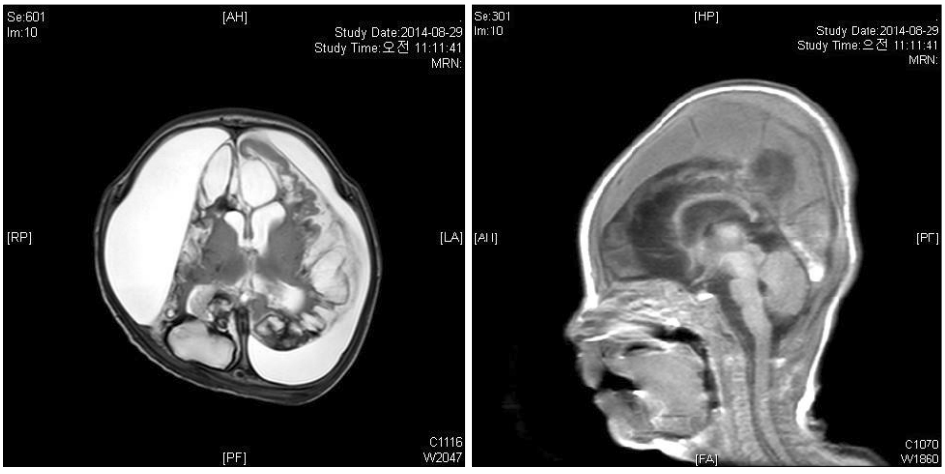

Fig. 2. Brain magnetic resonance imaging was done at 42 day of age; we found a large bilateral subdural hemorrhage, a subacute intracranial hemorrhage in the right parietal lobe, and suspected thrombi in the straight and bilateral transverse sinuses.

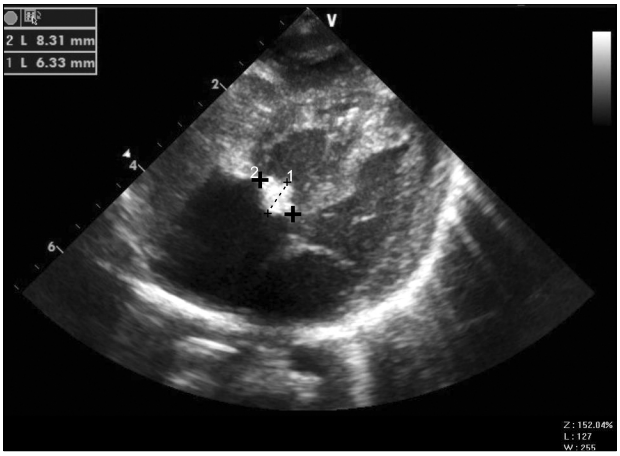

Fig. 3. An approximately 4×3 mm size thrombosis was found in the right ventricle as a round echogenic mass by echocardiography.

which was induced by heparin. We thus did not use heparin or warfarin in the patient's treatment. Aspirin, an antithrombotic agent, was the next choice as no additional thrombi occurred after birth. Other anticoagulants such as enoxaparin or direct thrombin inhibitors could have also been used. Cardiologists suggested that would be no beneficial to do thrombolytic therapy nor to do surgical removal of cardiac thrombus because it is not separated in small pieces to make distal embolism and it is not making valve obstructions and not making hemodynamic changes. Patient is bed ridden status with limited in daily movements, so we are just keep following echocardiography to find out whether cardiac thrombus size and hemodynamics change. We found no changes in cardiac thrombi and no thrombotic events until 1 year of age.

The patient was born to a single mother who initially refused further evaluation such as genetic analysis and further surgical treatment in the neonatal intensive care unit. As seizure onset typically occurs during the neonatal period, perhaps an early surgical intervention could have improved the patient's neurologic outcome. The patient was diagnosed with West syndrome and encephalomalacia later in the sequence of hemorrhagic brain damage. He is now 1 year of age and is followed by the pediatric neurology department of Severance Children's Hospital.

The patient's AT activity was below 20% at all times of the study; thus, we began to suspect an inherited AT deficiency. Genetic evaluation was initially refused but was undertaken during the maintenance of anticoagulation therapy. At 10 months of age, genetic analysis confirmed the deletion of coding and flanking sequences of SERPINC1 [c.235C>T (p.Arg79Cys) and c.442T>C (p.Ser148Pro)]. The p.Ser148Pro deletion was detected in the patient's mother but the other mutation was not. It is possible that this mutation was present in the father, but this supposition could not be confirmed.

Discussion

A high risk of venous thromboembolic disease is characteristic of type I AT deficiency. Although some cases of arterial TE in AT-deficient individuals have been reported, this association is much weaker. Venous TE typically occurs as deep vein thrombosis of the legs and arms, and pulmonary embolism, but can also occur in unusual sites, such as cerebral, sinus, mesenteric, portal, hepatic, renal, and retinal veins [7]. Cerebral thrombosis is a common finding, but cardiac thrombosis cases are rare; our case had both cerebral and cardiac symptoms. Binnetoglu et al. [8] described a 15-year-old female with AT deficiency in Turkey, and thrombi were found in the right renal vein and right ventricle of the heart, occluding tricuspid valve. Further reports are needed for rare thrombi in patients with AT deficiency and their resulting prognoses.

The risk of TE in an AT-deficient patient increases significantly around the age of 20 years; by the age of 50 years, approximately 50% of individuals with AT deficiency will have had an episode of venous TE [3]. In our case, a thrombotic event occurred during an unusual period. Homozygosity for AT deficiency could mean more thrombotic events early in life, but our case was a heterozygote. Kang et al. [9] described a case in Korea with neonatal seizure and residual encephalomalatic changes, including sinovenous thrombotic hemorrhages during the neonatal period due to AT deficiency. Further case reports with early thromboses should be reviewed.

Inherited AT deficiency is an uncommon autosomal-dominant disorder. Most cases are heterozygous. Homozygosity for AT deficiency is rare and almost always fatal in ute-

ro [1]. Ichiyama et al. described a p.Ser148Pro mutation that manifested as vasculitis in a 4-year-old patient [10]. In our case, the mutation was not homozygous, but the presence of two or more mutations (double allele, compound heterozygous) might have increased the risk of TE. For this reason, thrombogenic events might have an early onset, and further genetic investigation and review are needed.

The initial management of venous TE in patients with AT deficiency does not differ from that of venous TE in any other patient: initial therapy with heparin and transitioning to warfarin [11]. No data exist as to what the best treatment is for a patient with AT deficiency who has had an arterial thrombotic event [3]. In our case, the patient experienced a side effect of heparin, so we used aspirin therapy; no additional thrombotic events occurred until 1 year of age. De Stefano et al. [12] concluded that AT deficiency is an independent risk factor for recurrence and mark potential candidates for long-term oral anticoagulation. Further case reports are needed on alternative therapies and their prognoses.

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