A novel COL3A1 gene mutation in patient with aortic dissected aneurysm and cervical artery dissections

Abstract A considerable proportion of aortic aneurysms are shown to have genetic backgrounds. The COL3A1 gene, which encodes type III procollagen and causes Ehlers–Danlos syndrome (EDS) type IV, is one of the candidate genes associated with aortic aneurysms. The COL3A1 gene is also associated with cervical artery dissections (CAD) mostly as a part of manifestations of EDS type IV. We describe a 34-year-old Korean woman with both abdominal dissected aortic aneurysm and CAD accompanying atrial septal defect and multiple cysts in ovary and thyroid glands. She lacked cardinal manifestations of EDS type IV other than the vascular abnormalities, but molecular analyses of the COL3A1 gene confirmed a de novo heterozygous missense mutation that has not been reported before (c. 781G > A; Gly261Ser). This case suggested that the COL3A1 gene could be one of etiologically linked genes in isolated vasculopathies such as aortic dissected aneurysm or CAD, although being rare.

Key words COL3A1 · Aortic aneurysm · Cervical artery dissection · Ehlers–Danlos syndrome

Introduction

Aortic aneurysm is a common disorder characterized by a chronic degeneration of the aortic wall, often leading to death especially when ruptured. A considerable proportion of aortic aneurysms are shown to be familial and genetically associated, even when they are not associated with well-recognized heritable syndromes such as Marfan syndrome or Ehlers–Danlos syndrome (EDS) type IV. Many candidate genes for aortic aneurysms have been suggested. Among them, the COL3A1 gene encoding the type III procollagen is well known to be etiologically linked to the EDS type IV, which is characterized by four diagnostic criteria: extensive bruising, thin transparent skin, characteristic facial features, and rupture of the arteries, uterus, or intestine.

Spontaneous cervical artery dissection (CAD) is an important cause of ischemic stroke in young patients (<50 years). Although ultrastructural studies have found abnormalities in collagen fibrils from the skin biopsy specimens of about half of the patients with CAD, only a minority of these patients show clinical signs associated with known hereditary connective tissue disorders and familial cases with CAD are rare. On the other hand, patients with EDS type IV sometimes encounter with CAD, and the COL3A1 gene is the only gene hitherto proven to be associated with CAD mostly as a part of various vascular manifestations of EDS type IV.

To our knowledge, a few familial aortic aneurysm cases and only one familial cervical artery dissection case with COL3A1 mutations not showing other cardinal manifestations of EDS type IV have been reported thus far. In this report, we present clinical and genetic analysis results of a patient carrying both aortic dissected aneurysm and CAD with a de novo COL3A1 mutation, lacking other features of EDS type IV.

Case report

A 34-year-old Korean woman had accidentally been found to have abdominal aortic dissections and aneurysms on abdominal ultrasonography (US) during a general health examination in our hospital. She had symptoms of recurrent headache, radiating neck pain, and back pains. Physical
examination revealed a pulsating mass on the abdomen and carotid bruits on both sides of the neck. She was of normal height and had no Marfanoid skeletal features. Eye examination found no abnormalities of the lens. Her skin was of normal appearance with no visible vein or hyperelasticity, and her joints were not hypermobile. Neurological examinations showed no abnormalities. She had no histories of easy bruisability, intestinal perforation, or uterine rupture. While bearing two daughters, no complications associated with pregnancy or delivery were noted except for recurrent back pains. A 4-cm sized ovarian cyst was noted in transvaginal US but there were no disturbances in the balance of sexual or pituitary hormones. She was a nonsmoker and had no underlying diseases such as hypertension and diabetes. A family history of aortic aneurysm was not noticed either. Her laboratory data including serum lipid levels and coagulation profiles were all within normal limits.

Computed tomography (CT) angiography of thoracoabdominal aorta disclosed localized dissecting aneurysm of distal abdominal aorta (diameter: ∼2.6 cm) extending to both common iliac arteries with thrombi (arrow) in the false lumen of right common iliac artery. Computed tomography angiography of carotid arteries showed multifocal vascular lesions with arterial dissections, including right proximal vertebral artery and both distal internal carotid arteries (arrowheads) in the false lumen of right common carotid artery. Cervical arteries: arterial dissections of right proximal vertebral artery (arrow) and both distal internal carotid arteries (arrowheads).

Because a left-to-right shunt was noted, a transcatheter closure of the ASD using a 17-mm Amplatzer Septal Ocluder (AGA Medical, Golden Valley, MN, USA) was done without any complications such as bleeding, hematoma, or fistula. Shortly before the ASD device closure, thyroid US was performed and multiple anechoic cysts (∼0.3 cm) were noted on both thyroid glands; they looked benign with normal thyroid hormone levels. Abdominal US found a 1.5-cm sized low-echoic area on the left hepatic lobe, which was suspected to be a king of unusual hemangioma.

**Materials and methods**

**Sequence analysis**

Because the woman was young and had multifocal aneurysms, a connective tissue disorder was suspected and a genetic analysis by direct sequencing of all 51 coding exons