Novel Mutation in the Transforming Growth Factor Beta Receptor-1 Gene in a Patient with Cerebrovascular Fibromuscular Dysplasia

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Abstract

Background: Transforming growth factor beta receptor 1 and 2 (TGFBR1/2) mutations have been identified across a spectrum of clinical presentations, including familial thoracic aortic aneurysm and dissection (TAAD) and Loeys-Dietz syndrome (LDS). We report a novel mutation in the TGFBR1 gene in a patient with cerebrovascular fibromuscular dysplasia (FMD), arterial tortuosity, and thoracic aortic aneurysm.

Case Report: 71 year-old Caucasian woman followed for a spontaneous left vertebral artery dissection (age 67) and prominent beading of the distal left internal carotid artery consistent with medial-type FMD, no evidence of renal FMD. Cerebrovascular tortuosity was noted. Her father died at age 47 of unknown cause. She had no overt craniofacial or skeletal abnormalities. Subsequent CTA identified dilation of the ascending thoracic aorta (4.5 cm) with tortuosity of the descending thoracic aorta. Clinical testing for TGFBR1/2 mutations revealed a novel heterozygous point mutation in TGFBR1 (c.611 C>T, p.Thr204Ile).

Discussion: FMD is an uncommon vascular disorder of unknown etiology associated with arterial stenosis, dissection, and aneurysm. Mutations of the TGFBR1/2 gene have been associated with androgenetic arteropathy, aneurysm, and dissection. We report the case of an elderly patient with clinical and angiographic features of cerebrovascular FMD with arterial and aortic tortuosity, TAA, and a novel mutation of TGFBR1. Whether this case represents coincidence or a true association between this TGFBR1 mutation and angiographic changes of FMD is unclear. Regardless, the link between FMD and connective tissue abnormalities, particularly mutations of TGFBR1/2, require further exploration.

Introduction

- FMD is a nonatherosclerotic, noninflammatory vascular disease that can affect almost every artery.
- The cause of FMD remains unknown, however, a variety of genetic, mechanical, and hormonal factors have been proposed as possible contributors.
- TGFBR1/2 mutations have been associated with different disease presentations including TAAD and LDS.
- LDS is a recently described autosomal dominant genetic syndrome characterized by vascular findings and skeletal, craniofacial and/or cutaneous manifestations.

Patient Description

71 year-old Caucasian Female

- With a past medical history significant for hypertension and migraine headaches
- At age 67 she presented to her local physician with an acute episode of non-positional vertigo associated with parasthesias over her left face, neck and arm.
- Subsequent workup revealed significant beading in the distal LICA consistent with medial-type FMD, cerebrovascular tortuosity and a left vertebral artery dissection
- Duplex ultrasound imaging of her renal and mesenteric arteries found no evidence of FMD.
- Referred to our center for a second opinion
- On physical exam, the patient was above average in terms of height (175.3 cm) but did not have any overt craniofacial, skeletal or cutaneous abnormalities
- Given her significant arterial tortuosity and aortic dilation, we proceeded with molecular genetic testing and sequence analysis of TGFBR1 and 2

Findings

- FMD is an uncommon vascular disorder of unknown etiology associated with arterial stenosis, dissection, and aneurysm.
- Genetic factors may play a role in the pathogenesis of FMD as the disease has been observed among the first degree relatives of persons affected with renal FMD.
- Previously, McDonnell et al. identified a cohort of 30 patients with FMD and varying features of Ehlers-Danlos syndrome (EDS) without TGFBR1/2 or COL3A1 gene mutations. It was concluded that there might be a previously unrecognized connective tissue disorder that presents with FMD as its major clinical feature.
- There is a wide variety of different clinical presentations associated with TGFBR1/2 mutations. They all seem to share a propensity to dissection and dilation of larger arteries at any age.

Conclusion

To our knowledge, we report the first case of an elderly patient with clinical and angiographic features of cerebrovascular FMD with arterial and aortic tortuosity, TAA, and a novel heterozygous point mutation of TGFBR1.

Our patient's missense gene mutation resulted in threonine being replaced by isoleucine at position 204 of the TGFBR1 protein. There are no reports of this mutation in other species indicating its probable functional significance. Loeys et al. reported the same type of substitution at a nearby position within the junction region (p. Thr200Ile) in a child with LDS.

Whether this case represents coincidence or a true association between this TGFBR1 mutation and angiographic changes of FMD is unclear. Regardless, the link between FMD and connective tissue abnormalities, particularly mutations of TGFBR1/2, require further exploration.

References