Case Report

Discovery of a Novel Mutation in the REN Gene in Patient With Chronic Progressive Kidney Disease of Unknown Etiology Presenting With Acute Spontaneous Carotid Artery Dissection

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Most dissections of extracranial arteries involve some mechanical stress or connective tissue abnormalities. In the absence of these disorders, determining the etiology is challenging. Genetic factors may play an important pathophysiologic role. We report on a 36-year-old male with the right internal carotid artery dissection and a novel genetic variant in the REN gene. Our report offers evidence that mutations in the REN gene could have pathogenic role in arterial dissection. The subject gave written informed consent for the publication of this case report. The authors declare no conflict of interest.

Key Words: Cervical artery dissection—autosomal dominant tubulointerstitial kidney disease—genetic risk factors—genetic risk factors

Introduction

Spontaneous extra- and intracranial arterial dissections may be caused by genetic and environmental factors, each having a modest and potentially synergistic effect.[1] Genetic factors have an important role in the pathophysiology of cervical artery dissection (CAD), in rare cases as part of a single gene disorder and more commonly as part of a multifactorial predisposition.[2] CAD has been described in genetic forms of renal disease. Autosomal dominant tubulointerstitial kidney disease associated with REN gene mutation (ADTKD-REN) is a rare disease with less than 20 families reported worldwide. Individuals suffer from hypouricosuric hyperuricemia, uric arthritis and renal impairment that usually leads to end stage renal failure. Genetic analysis of the REN gene should be used to place a diagnosis.[3]

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Case Report

We report on a 36-year-old male with acute onset of headache, Horner syndrome and a history of etiologically undefined renal insuficiency without arterial hypertension. The patient did not have signs that could be pointing to one of the connective tissue disorders. When he was 20 years old, uric arthritis was diagnosed. Renal insufficiency with reduced estimated glomerular filtration rate (eGFR 61 mL/minute/1.73 m^2), elevated serum creatinine levels (S-creatinine 127μmol/L) and hyperuricemia (S-uric acid 545 μmol/L) were observed. The urinalysis was bland with trace proteinuria (U-protein 0.16 g/L), with no cells, casts or uric acid crystals. Other laboratory tests, including 24-hour urine uric acid level, thyroid hormones, vitamin B12, folic acid, and rare protrombogenic risk factors were within normal limits. Computer tomography angiography showed right internal CAD with pseudoaneurismatic extension at the C1 vertebral level (Fig 1). Renal fibromuscular dysplasia was excluded using duplex ultrasound. Transthoracic echocardiography did not detect congenital heart defects. Prophylactic therapy with acetylsalicylic acid was introduced.

His grandfather and uncle also had chronic kidney disease (CKD) of unknown etiology. We decided for genetic

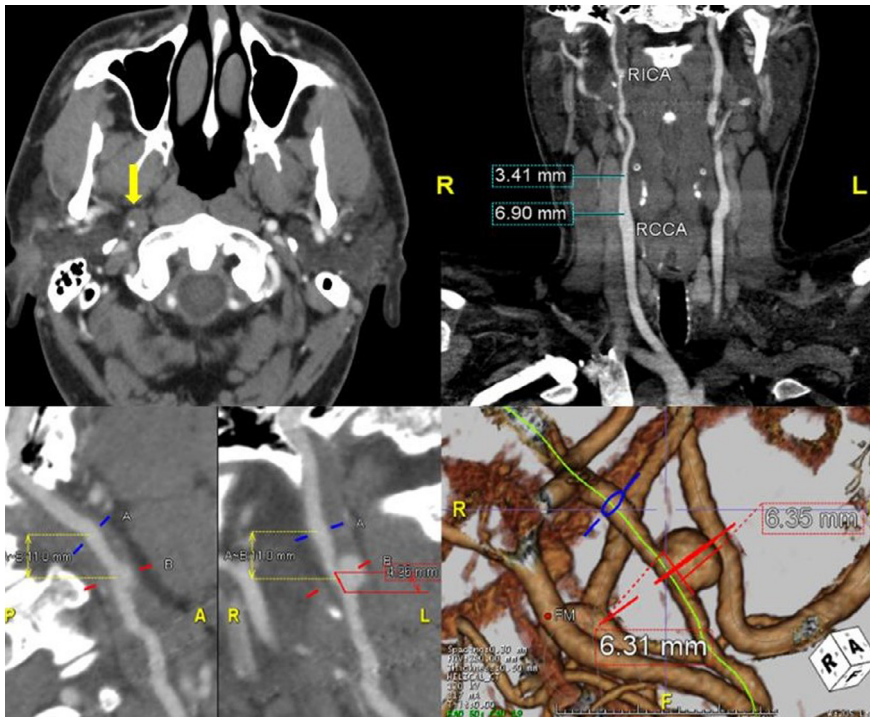

Figure 1. *Computer tomography angiography showed right internal CAD (yellow arrow) with pseudoaneurismatic extension at the C1 vertebral level.*

testing that included 32 genes. Clinical exome sequencing showed a genetic variant of uncertain significance in the REN gene in the heterozygous state (NM_000537.3: c.255G> C; p.Gln85His). ADTKD-REN was diagnosed. The subject gave written informed consent for the publication of this case report.

Discussion

The CAD has been associated with neck trauma, infection, hyperhomocysteinemia, migraine, hypertension, and fibromuscular dysplasia.[2] All of the above mentioned risk factors have been excluded in our patient. Arterial dissections have been described in other genetic forms of renal disease,[4] but not yet in patient with ADTKD. Pathogenic heterozygous variants in the REN gene represent a well-known cause for the ADTKD-REN. Its pathological effect in heterozygous form has not yet been described. The clinical exome sequencing in our study did not show the presence of any other genetic variants that could explain the clinical picture.

The REN gene encodes preprorenin, that is proteolytically processed to produce prorenin and subsequently renin.[5] Renin is a protease that cleaves angiotensinogen to angiotensin and stimulates aldosterone production. Mutations in the REN gene lead to intracellular accumulation of abnormal protein, resulting in apoptosis of renin-producing cells.[6] The mutations in the REN gene thus have the effect on renin-angiotensin system (RAS). RAS has been described that could have a role in the development of an aneurysm of thoracic and abdominal aorta, but not yet in arterial dissection.[7] Recently a novel mutation in NOTCH1 gene was reported in patient with spontaneous dissections of extracranial arteries. According to some studies the NOTCH signaling pathway is involved in the control of renin gene exspresion.[8] Its link with developmental pathways of the human cardiovascular system suggests that this variant could be disruptive in the extracellular matrix of extracranial arteries in nonsyndromal extracranial artery dissections.[9] Considering this, our report offers evidence that mutations in the REN gene could play the possible pathogenic role in arterial dissection through the effect on the RAS system. However, according to the current data, we cannot definitively determine the causative role of the established genetic variant in the presenting clinical picture.

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