Clinical/Scientific Notes

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ACUTE URINARY RETENTION DUE TO A NOVEL COLLAGEN *COL4A1* MUTATION

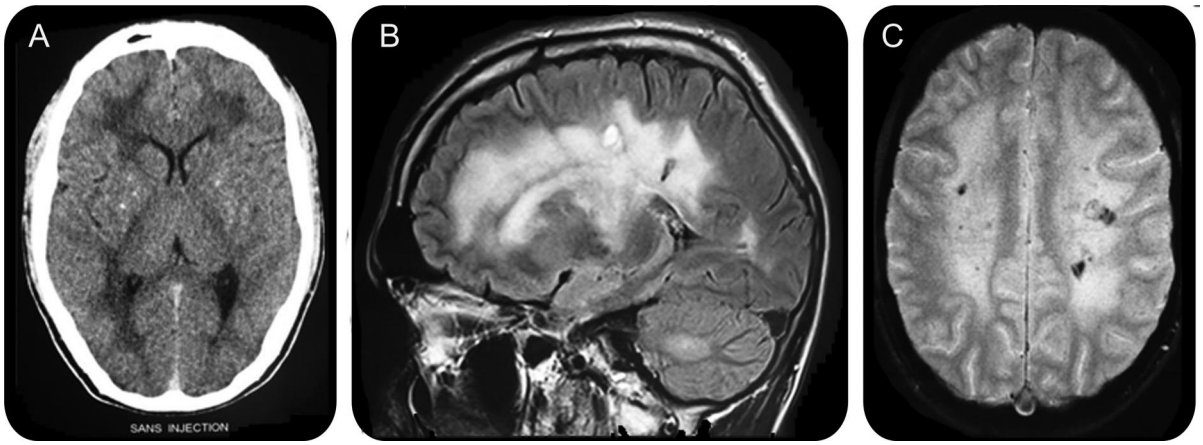
The gene *COL4A1* encodes the α1 chain of type IV collagen, a basement-membrane protein implying vascular parietal strength. Mutations in the gene *COL4A1* have been described in families with diffuse small-vessel disease of the brain, resulting in perinatal stroke, congenital porencephaly, extensive leukoencephalopathy, intracerebral hemorrhage, and retinal arteriolar tortuosity.[1-4] Our observation extends the clinical and magnetic resonance (MR) phenotype of *COL4A1* mutation.

Case reports. A 21-year-old man without neurologic medical history presented with acute urinary retention. He had a right amblyopia due to a congenital strabismus surgically treated in childhood. Clinical examination showed brisk lower limb reflexes and a left Babinski sign. Blood pressure was normal. The Mini-Mental State Examination score was strictly normal. The patient declined further neuropsychological testing. Brain CT showed diffuse leukoencephalopathy and multiple supratentorial microcalcifications (figure, A). Brain MRI revealed widespread white matter hyperintensities on T2 and fluid-attenuated inversion recovery sequences, dilated perivascular spaces, and lacunar infarctions. Leukoencephalopathy involved the cerebral periventricular and cerebellar deep white matter (figure, B). Multiple microbleeds were seen on gradient echo sequences, involving brainstem and supratentorial white matter (figure, C). MR angiography of cervical and intracranial arteries was normal, as was spinal cord MRI. Results of extensive biologic investigations, including complete blood count, serum electrolytes, liver enzymes, creatine kinase level, coagulation tests, serum homocysteine, anticardiolipin antibodies, lupus anticoagulant, antinuclear factor, creatinine clearance, lysosomal enzyme activity, and very long chain fatty acids, were normal. Microalbuminuria and hematuria were absent. Electrocardiography, transthoracic echocardiography, and cervical and renal ultrasound examination results were normal. Results of research for mitochondrial disorder (electromyography; study of the mitochondrial respiratory chain on muscle biopsy; mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes [MELAS], myoclonic epilepsy with ragged red fibers [MERFF], and Leigh mutations) were negative. Notch3 gene mutation, in search for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), was negative. Ophthalmologic examination revealed an asymptomatic left posterior capsular cataract, without retinal arteriolar abnormalities. A mutation of the *COL4A1* gene was found (c.2263G>A, exon 30), responsible for a glycine-to-arginine substitution (p.G755R) within the triple-helix domain of the *COL4A1* gene. This mutation was not present in 288 control chromosomes.

The patient's relatives had no medical history of neurologic disorders. Both parents had normal clinical examination results. In addition, they did not carry the G755R *COL4A1* gene mutation. Our patient had 1 brother (age 27 years) and 1 sister (age 17 years), who were asymptomatic. At 1 year follow-up, clinical and ophthalmologic examinations of the patient remained unchanged, and brain CT showed no evidence of progression of cerebral abnormalities. Treatment included self-catheterization for urinary retention and avoidance of risk factors for bleeding, such as hypertension and exercise-induced stress. Antiaggregant and anticoagulant therapy was contraindicated because of the risk of hemorrhagic strokes.

Discussion. Type IV collagen is a major component of almost all basement membranes, including vascular basement membrane. Six different α chains belong to the family of type IV collagen molecules, which can form 3 different networks: α1.α1.α2 (IV), α3.α4.α5 (IV), and α5.α5.α6 (IV).[5] Mutations in α3 (*COL4A3*), α4 (*COL4A4*), and α5 (*COL4A5*) are associated with the Alport syndrome. Mutations in the *COL4A1* gene were described for the first time in 2005 in mutant mice with severe cerebral hemorrhage occurring during the perinatal period and adult-onset hemorrhagic stroke in small-penetrating-vessel regions.[1,2] In humans, clinical phenotypes of

Figure Brain CT and MRI of the patient



(A) CT scan: diffuse leukoencephalopathy and multiple micro calcifications. (B) Sagittal fluid-attenuated inversion recovery imaging: diffuse periventricular and cerebellar leukoencephalopathy, and a dilated periventricular space. (C) Axial gradient echo sequence: multiple round hypointensities in the white gray matter suggestive of microbleeds.

autosomal dominant *COL4A1* mutations include cerebral and retinal small-vessel disease, hereditary porencephaly, hemorrhagic stroke, or silent microbleeds.[1-3] Diffuse leukoencephalopathy and deep lacunar infarctions associated with anterior eye chamber developmental anomalies of the Axenfeld-Rieger type were also reported.[6] Another phenotype associated with *COL4A1* mutation has recently been reported under the acronym HANAC (hereditary angiopathy, nephropathy, aneurysms, and muscle cramps), including asymptomatic intracranial aneurysms.[7] *COL4A1*-associated MR abnormalities include diffuse leukoencephalopathy, microbleeds, dilated perivascular spaces, porencephaly, and deep intracerebral hemorrhages.

COL4A1 mutations mainly affect a glycine residue in the triple-helix domain of the protein,[1,2,6] leading to alterations of the vascular basement membrane.[2] The mutation identified in our patient has already been described in a family, causing childhood onset recurrent strokes and cataracts.[4] The mechanisms underlying the wide phenotypic variability associated with *COL4A1* mutations remain unknown.

Our report extends the clinical and neuroradiologic phenotypes of *COL4A1*-related diseases: urinary retention in adulthood, de novo mutation, brain calcifications, severe leukoencephalopathy, cerebellar white matter changes, and absence of porencephalic cavities. We suggested that the *COL4A1* genetic screening should be proposed mainly in young patients with vascular leukoencephalopathy and hemorrhagic stroke or silent microbleeds of unknown etiology, in the absence of hypertension, even without any family history of neurologic manifestations.

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