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LETTER TO THE EDITORS

‘De novo’ Col4A2 mutation in a patient with migraine, leukoencephalopathy, and small carotid aneurysms

Paul Kollmann[1,2] · André Peeters[3] · Olivier Vanakker[4] · Yves Sznajer[5]

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Dear Sirs,

Collagen IV-related diseases affect the basement membrane and can be caused by COL4A1 or COL4A2 gene mutations. The phenotypic expression seems to be similar in both and encompass porencephaly, small-vessel disease, ocular involvement, peripheral myopathy, and kidney disease.

A 17-year-old boy presented with migraine headaches for 5 years. A brain MRI showed diffuse white matter hyperintensities on FLAIR sequence, while MRA revealed small aneurysms of both carotid siphons (Fig. 1). He had a completely normal physical exam. He never complained of muscular cramps, but a severe transient increase in CK level (9 70 the normal range) was recurrently measured 24–72 h after mild exercise (football). Myoglobinuria was ruled out at rest. Abdominal MRI and ophthalmologic examination with uorescein angiography were normal. Sequencing of COL4A1 did not identify any mutation. COL4A2 gene sequencing identi ed the c.2105 G A substitution: p.(Gly702Asp). This mutation has been found in a large family showing dominant porencephaly with reduced penetrance [1, 2]. The present report adds a distinct patient of Caucasian origin with the same mutation: this allows to con rm its pathogenicity (after molecular evidence—nucleotide and protein changes as impact on the triple helix formation—and cellular involvement). His healthy parents did not carry the mutation (‘de novo’). After 1-year follow-up, brain MRI and MRA remained unchanged.

Type IV collagens are a major component of all basement membranes. Six genes arranged by pairs encode for six alpha polypeptide chains. The COL4A2 gene encodes the alpha 2 polypeptide chain which forms heterotrimers with two alpha 1 chains. Each polypeptide chain contains a triple helical domain, a short 7S domain and a globular non-collagenous (NC1) domain. The collagenous domain consists of Gly-Xaa-Yaa repeats with interruptions. Putative COL4A2 gene mutations were found on X location of the repeats and in the NC1 domain in patients suffering from intra-cerebral haemorrhage (ICH) [3]. Signi cant differences in phenotypic expression of an individual mutation also suggest a role for environmental in uences or genetic modi ers with a focus on the secretion’s regulation of mutant COL4A2 from the endoplasmic reticulum [1]. Phenotypic variability (ICH, myopathy, etc.) seems to depend on different pathogenic mechanisms, and their respective severity may be correlated to the different locations of the mutation [4]. Increase CK level without cramps is well known in patients with HANAC syndrome [5]. A link between CK elevation and exertion has never been reported in patients with COL4A2 gene mutation but was reported in mice with COL4A1 gene mutations [6]. De novo mutations were found in two other patients [7, 8]. Our patient is up to now asymptomatic similar to adult carriers

& Paul Kollmann
paul.kollmann@chirec.be

1 Department of Neurology, CHIREC, Nouvelle Clinique de la Basilique, 37-47 Rue Pangaert, 1083 Brussels, Belgium

2 93 rue d’Anderlues, 7141 Carnières, Belgium

3 Department of Neurology, Cliniques Universitaires St-Luc, Université Catholique de Louvain, 10 Av. Hippocrate, 1200 Brussels, Belgium

4 Center for Medical Genetics, Ghent University Hospital, 185 De Pintelaan, 9000 Ghent, Belgium

5 Center for Human Genetic, Cliniques Universitaires St-Luc, Université Catholique de Louvain, 10 Av. Hippocrate, 1200 Brussels, Belgium

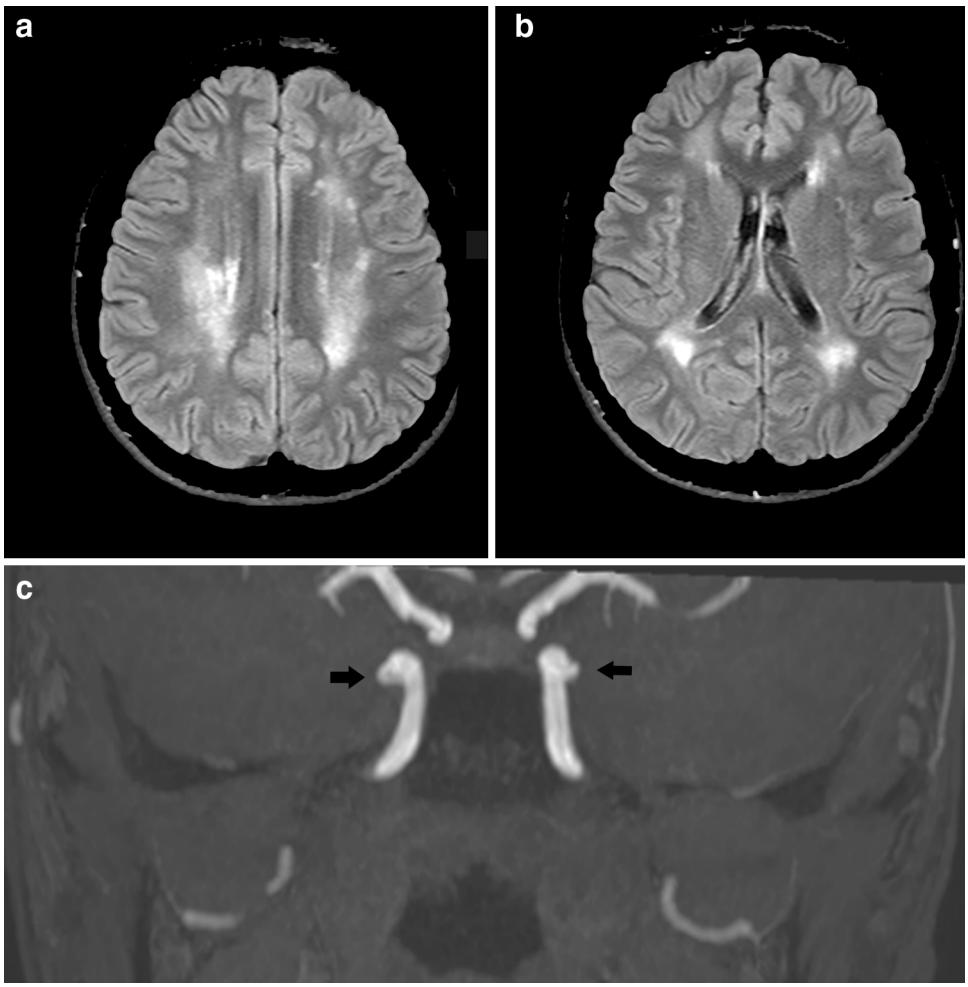

Fig. 1 Brain MRI (FLAIR sequence) shows leukoencephalopathy (**a**, **b**), and brain MRA shows small aneurysms of both carotid siphons (1.8 and 3.5 mm diameter) (**c**)

already identified [1, 2, 7, 9], but a carrier with the same mutation did not show any MRI anomaly suggestive of cerebral small-vessel disease at the time of the report (1–2) and in one sporadic patient (de novo mutation) a first deep ICH occurred at age 23 [8]. When considering the mutation's location near the C terminus of the triple helical domain, this may suggest a higher haemorrhagic risk [4]. An increase of ICH risk induced by intense exercise was recorded [4]. Two patients with *COL4A1* gene mutation and one with *COL4A2* mutation presented with ICH triggered by exercise [8, 10, 11]. Whether presymptomatic recommendations in patients with Collagen type IV mutations should address the caution for intense exercise still needs to be validated.

The finding of leukoencephalopathy and/or carotid siphon aneurysms in a patient should warrant *COL4A1* and *COL4A2* gene sequencing, even without a typical cerebral stroke event or family history. The case presented underlines the need for a comprehensive systemic evaluation, including CK quantification at rest and after exercise as well as ophthalmologic and kidney evaluation. Genetic counselling has to be provided to patients and (over time with better phenotype delineation and correlation) even in asymptomatic carriers.

Compliance with ethical standards

Ethical standards Patient gave informed consent and details that might disclose the identity of the patient have been omitted. This case has been done in accordance with ethical standards stated in the 1964 Declaration of Helsinki and its later amendments.

Conflicts of interest None.

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