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COL4A1 MUTATION: EXPANSION OF THE PHENOTYPE

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Background: *COL4A1* is a major basement membrane component, providing basement membrane stability. Mutations in *COL4A1* lead to a small-vessel brain disease, sometimes associated with renal disorders, cataract and tortuosity of the retinal vessels. *COL4A1*-related cerebral stroke is considered to result from thrombosis preferring deep venous structures in the brain.

Results: Mutations in *COL4A1* were diagnosed in seven infants, antenatally in one, who presented at 20 weeks of gestation with an intraventricular and a cerebellar haemorrhage; postnatally in the other six, either in the perinatal period (n=3) or in infancy (n=3). Unilateral porencephaly (PC) was present in four and was recognised at birth in three and at seven months in one. Two were preterm born sibs, showing a PC with resolving clots in the lateral ventricles. The third one with PC, presented at seven months with familiar hemiplegia. More severe cerebral stroke of antenatal onset was seen in two infants, with ventriculomegaly at 26 and 37 weeks gestation respectively. They had severe supratentorial as well as infratentorial lesions with severe cerebellar atrophy. Outcome was poor, with early death in two, severe cerebral palsy in three and moderate hemiplegia in one. The pregnancy with the affected child was still ongoing. In two infants the mutation in COL4A1 was inherited, in one the mother had a somatic mosaicism, the others had a *de novo* mutation of the *COL4A1*-gene, affecting different exons.

Conclusion: *COL4A1* mutation should be considered in the fetus with antenatal haemorrhage, newborns with PC and children presenting with (familiar) hemiplegia.