Intracerebral Hemorrhage and *COL4A1* Mutations, from Preterm Infants to Adult Patients

Intracerebral hemorrhage (ICH) accounts for 10% of stroke and is a particularly severe form of stroke. Therapeutic tools are still limited, and prevention remains the most important way to reduce morbidity and mortality. However, for effective prevention, we need to understand the factors underlying the occurrence of hemorrhagic stroke and to identify individuals at greatest risk. Hypertension is a leading factor for ICH in adult patients, and cerebrovascular malformations are the most common causes of ICH in children. However, ICH is a heterogeneous condition, and in a substantial proportion of ICH patients, particularly in the younger ones, no cause can be identified despite extensive investigations.

Recently, mutations of *COL4A1* have been shown to cause ICH and porencephaly both in mouse and human.[1–8] *COL4A1* encodes the α1 chain of type IV collagen, a major component of basement membranes, including vascular basement membrane. Mutated mice and human patients show an increased fragility of brain vessels that renders them highly sensitive to environmental factors such as birth trauma or antithrombotic agents. Gould and colleagues[1] previously showed that surgical delivery of mouse pups dramatically reduces the risk for cerebral bleeding in the perinatal period and suggested that caesarean delivery may decrease the risk for ICH in human neonates.

In this issue, de Vries and coworkers[9] report on two siblings born preterm, at 33 weeks, and at 31 weeks of gestation, with a very low birth weight and in whom perinatal cranial routine ultrasound and magnetic resonance imaging (in the second infant) detected resolving hemorrhages and porencephalic cavities. Both siblings carry a deleterious mutation affecting a glycine residue located in the second C-terminal tandem repeated domain of *COL4A1* α1 chain. This mutation was inherited from their asymptomatic mother. The presence of these lesions in the first days of life strongly suggests that these hemorrhagic events occurred antenatally and not during vaginal delivery. If these two preterm infants would have been delivered at term, one would assume that they might have been diagnosed later on as having congenital hemiplegia.[10]

The first obvious and important implication of this observation is that caesarean delivery would not be sufficient to completely prevent the occurrence of ICH in mutated infants. The second one is that prevention and genetic counseling are important in this condition. This observation raises a number of questions of interest not only for neuropediatricians, obstetricians, and geneticists but also for neurologists taking care of adult patients. One major question is when should we suspect a *COL4A1* mutation and conduct a genetic testing in a preterm or at-term infant showing an ICH. This question is not only important for medical care and genetic counseling but has also medicolegal implications. Currently, in cases of a familial porencephaly (more than one affected case), genetic screening of COL4A1 should be considered mandatory and will be of great help for genetic counseling. However, there are many situations in which the answer is so far unclear. Presumed antenatal or perinatal onset of a unilateral intraventricular/ICH leading to a porencephalic cyst is observed in 5 to 8% of very-low-birth-weight infants. Should all these infants be tested for *COL4A1* mutations in the absence of any affected relative and any other known causative factor? What should be done when intracranial bleeding is detected in utero by ultrasound screening?[11]

Another major question is when should we suspect a *COL4A1* mutation in an adult patient, who would then be at risk for ICH and at risk to have an affected child? *COL4A1* mutations lead to a number of distinct phenotypes both in mouse and human, depending on the genetic background or environmental factors, or both. Relatives of familial porencephaly children have been shown to have leukoencephalopathy and an increased risk for ICH and/or cerebral microbleeds and/or ischemic lacunar infarcts. Another autosomal dominant condition characterized by the association of arteriolar retinal tortuousities, infantile hemiplegia, and leukoencephalopathy has been associated with a *COL4A1* mutation.[12] A distinct phenotype associating anterior eye chamber developmental anomalies including congenital cataract, leukoencephalopathy, ischemic lacunar infarcts, and microbleeds has been reported in a *COL4A1*-mutated family.[13] At last, a novel phenotype associated with *COL4A1* mutations has recently been reported under the acronym HANAC (hereditary angiopathy nephropathy aneurysms and muscle cramps).[14] Screening of *COL4A1* is clearly indicated when a patient with hemorrhagic stroke and leukoencephalopathy has suggestive associated symptoms such as retinal arteriolar tortuosity and/or hematuria, or has a history of infantile hemiplegia with porencephaly and/or anterior eye malformation, regardless of whether the proband has affected relatives. However, associated symptoms are often missed, particularly in relatives. *COL4A1* muta-

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tions may also be detected in patients showing ICH and leukoencephalopathy without any other symptom or magnetic resonance imaging anomaly (M. Mine and E. Tournier-Lasserve, unpublished data). Interestingly, the grandfather of the two siblings reported in this issue of *Annals* died at age 52 years after a severe ICH without any previous history of hypertension. Although he was not tested for the *COL4A1* mutation present in his two grandchildren, his magnetic resonance imaging results strongly suggest that he was affected by the same disease.

Identification of *COL4A1* mutation carriers has important health and genetic counseling implications. These carriers have an important risk for antenatal or perinatal cerebral bleeding. Prenatal diagnosis is often required by young parents who have a child affected and plan to have other children. Prevention in older children and adults is important (no violent contact sports, no prolonged exercise, caution when an anticoagulant therapy is required). The clinical phenotype is heterogeneous, and this condition is most likely underrecognized. However, genetic screening of this large gene is time consuming and expensive, and additional work is needed to better delineate indications for genetic screening, particularly in patients with ICH and leukoencephalopathy without other symptoms or a relevant family history. A number of additional questions concerning the possible genotype phenotype correlations in this clinically heterogenous condition and the mechanisms leading to ICH and leukoencephalopathy will also need deeper exploration.

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Dystonia-Parkinsonism Disease Gene Discovery: Expect Surprises

Identifying a new disease gene often leads to direct tangible benefits, the most immediate of which is diagnostic molecular testing. The more distant benefits include improved understanding of disease pathophysiology and novel therapies based on the new genetic information, which are realized only after many years. During the inevitable gap in time between gene discovery and effective therapy, our clinical world undergoes a tumultuous upheaval as our "pregene" thinking meets our "postgene" knowledge. We strive to reorder and align in entirely new ways. After the identification of a new disease gene, the first surprise (and disappointment) often is that genotype is a weak predictor of phenotype. Next, patients considered to have the same disease are found to have mutations in other genes (the phenomenon of genetic heterogeneity), which complicates diagnostic testing. Further confusion ensues, challenging dogma and mocking our nosologies, when patients with wildly disparate phenotypes are shown to have mutations in the same gene. This phenomenon of allelic heterogeneity throws our clinical thinking into disarray and spurs a conceptual reorganization of how