Genetic of Intracranial Haemorrhage

Subjects: Reproductive Biology
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Fetal Intracranial hemorrhage (ICH) can be accurately identified in utero and categorized by antenatal sonography and/or MRI. Infectious disease, maternal drug exposure, alloimmune thrombocytopenia, maternal trauma, coagulation disorders and twin-to-twin transfusion syndrome can cause fetal ICH.

Keywords: hemostatic genes ; collagen genes ; X-linked-GATA1 genes

1. Introduction

Intracranial hemorrhage (ICH) is reported in premature infants but may rarely occur in prenatal life as well. The reported incidence of in utero ICH varies from 1/100,000 up to 1/1000 [1]. The classification of ICH includes five types according to the site of the lesion: intraventricular (IVH), subarachnoidal, intraparenchymal, cerebellar and subdural hemorrhage. IVH is the most common variety of neonatal ICH, due to the characteristics of the immature brain. They are subdivided into four grading, based on the extent of the lesion: the first three grades are limited to the ventricles, while the fourth grade includes parenchymal involvement. Fetal ICH can be accurately identified in utero and categorized by antenatal sonography and/or MRI. Ultrasounds are the modality of choice in the diagnostic pathway of fetal ICH, especially in IVH variants.

Typical ultrasonographic signs of IVH are various degrees of ventriculomegaly with irregular bulky choroid plexus; hyperechogenic, sometimes indented ventricular walls; intraventricular hyperechogenic foci suggesting clots; a subependymal hemorrhage manifesting as periventricular echodensities; and an intraparenchymal hemorrhage appearing as irregular echogenic brain mass, whereas under normal circumstances non-echogenic images would have been visualized (such as thalami). A subdural hemorrhage is easily recognized due to the presence of an echogenic area representing the hematoma that displaces the Sylvian fissure from the inner table of the skull, and finally, in the case of intracerebellar hemorrhage, the ultrasonographic findings included abnormal echogenicities within the posterior fossa [1].

Among the possible etiologies of fetal ICH, we can list infectious disease, maternal drug exposure, alloimmune thrombocytopenia, maternal trauma, coagulation disorders and twin-to-twin transfusion syndrome. However, in many cases, the cause may not be identified, and a condition arising from a genetic disorder, associated with an increased risk for cerebral arteriopathy, should be taken into consideration. Genetic causes of fetal ICH include:

- Hemostatic genes: von Willebrand's disease, congenital factor V, factor VII, factor VIII and factor X deficiency and protrombotic disorders (factor V Leiden, MTHFR mutation, protein C deficiency);
- Inflammatory genes: polymorphisms in the pro-inflammatory cytokine IL-6;
- Collagen genes: COL4A1 and COL4A2 mutations;
- X linked GATA1 gene mutation.

2. Genetic Profiling of Idiopathic Antenatal Intracranial Haemorrhage

Table 1 shows the data of genetic profiling of idiopathic antenatal intracranial Haemorrhage. With regard to the etiology of this disease, when common causes of fetal ICH cannot be identified, clinicians classify ICH as idiopathic. However, several gene mutations have been found to be associated with this condition, although only a few authors have investigated genetic profiling and reported single cases (Table 1).

Table 1. Genetic causes of fetal intracranial haemorrage: incidence, inheritance and numbers of case reports.

Etiology	Incidence	Inheritance	Case Reports
Haemostatic genes			
Factor V deficiency	1/1,000,000	autosomal recessive	2
Von Willebrand's disease	1/100–1/1000	AD (type 1-2) and AR (type 2-3)	1
Factor VII deficiency	1/300,000–1/500,000	incompletely recessive autosomal	1
Protrombothic disorders			
Polymorphism MTHFR gene	3/100–3,7/100	autosomal recessive	1
Factor V Leiden variant	3/100	autosomal dominant	3
Prothrombin 20210G>A variant	3/100–5/100	autosomal dominant	0
Protein C deficiency	2/1000–5/1000	autosomal recessive	2
Collagen genes			
COL4A1 and COL4A2	6–7/100,000	autosomal dominant	20
GATA1 gene mutation			
	<1/1,000,000	X-linked	1

Sonography is the diagnostic modality of choice. However, since ultrasound has low sensitivity for minor hemorrhages, magnetic resonance imaging (MRI) is routinely carried out to confirm the presence of ICH; moreover, MRI can go a long way towards establishing time and evolution of the bleeding. Sonographic evidence of a fetal intracranial hemorrhage hinges upon the timing of the ultrasound related to the incident. If the bleed begins within 24–48 h of the ultrasound, hyperechoic signals without posterior shadowing should be detectable [2]. ICH diagnostic pathways may prove essential in terms of staving off malpractice charges and adverse litigation results. The diagnostic process, it should be kept in mind, is not a "binary relation" always capable of establishing pathological conditions. Most fetal intracranial hemorrhages are detected at routine prenatal sonography. Most cases, often of high grade, are discovered over the third trimester. Postnatal survival rates are considerably high, but so is the risk of adverse neurologic outcome in most neonates [3].

Demonstrating the genetic etiology in neonates born with in utero ICH classified as idiopathic, allows us to acknowledge this event as unpreventable. To identify the genetic cause of ICH can also guide the counselling about the possibility of recurrence risk in the same family.

3. Summary

When fetal hemorrhage is diagnosed, a prompt inquiry into the genetic profile of disorders related to ICH must be performed, beginning from family history. A stillbirth with intracranial hemorrhage may result from an unrecognized factor deficiency or mutation. There are genetic aspects to take into consideration in case of fetal ICH like demonstrating that this condition was not preventable. However, in case other causes are excluded or in case of recurrence in the same family, genetic profiling could be investigated.

4. Conclusions

When fetal hemorrhage is diagnosed, a prompt inquiry into the genetic profifile of disorders related to ICH must be performed, beginning from family history. A stillbirth with intracranial hemorrhage may result from an unrecognized factor defificiency or mutation. There are genetic aspects to take into consideration in case of fetal ICH like demonstrating that this condition was not preventable. In conclusion, it is ethically appropriate to provide parents with a thorough risk assessment as to the prospects of recurrence in future pregnancies [38]. We do not suggest this genetic profifiling routinely and we need more consistent data to select a target population in which this analysis could be useful. However, in case other causes are excluded or in case of recurrence in the same family, genetic profifiling could be investigated. We need an international collaboration to collect all cases affected by fetal ICH related to these genetic causes in a database[4].

References

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