FETAL INTRAVENTRICULAR HEMORRHAGE OF GENETIC ETIOLOGY

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INTRODUCTION

Fetal intraventricular hemorrhage (IVH) is an important cause of infant morbidity and mortality, resulting in different degrees of **neurodevelopmental disability**, including developmental delay, motor impairment, epilepsy and, in extreme cases, fetal or neonatal death. Fetal IVH is rare, with an estimated incidence of 1 in 10,000 pregnancies.

IVH results from the **bleeding of the germinal matrix**, an immature capillary network underneath the ventricular ependyma, present in 24 to 32 weeks fetuses. Its rupture can occur as a consequence of the fragility of the vasculature, brain blood flow disturbance, acidosis or coagulation disorders. There are many maternal and fetal factors associated to IVH, such as thrombocytpenia and fetal coagulation disorders, infections, severe fetal hypoxia, etc. However, most cases occur sporadically and in those, the recurrence is extremely rare. When the cause is not identified, a genetic disorder should be taken into consideration.

The **ultrasound diagnosis** is difficult. If the hemorrhage is recent, it will appear as an echogenic mass without posterior shadowing. Over time, the appearance becomes more heterogeneous. The association to **ventriculomegaly** is due to the **obstruction of cerebrospinal fluid circulation** because of blood cell detritus. IVH may also produce obstruction of the terminal veins, with venous congestion and the development of hemorrhagic venous infarction.
There are four **grades of IVH**, adapted from the Papile grading system: (I) hemorrhage restricted to the germinal matrix and ependyma, (II) hemorrhage affecting lateral ventricles by less than 50% of ventricular area, (III) if it associates ventricular dilatation and occupying more than 50% of the ventricle area and (IV) when it involves white matter, causing a periventricular hemorrhagic infarction (PVHI).

We present the case of a patient who had **two consecutive pregnancies with a prenatal diagnosis of intraventricular hemorrhage (IVH)** at the Son Espases University Hospital of genetic origin. We have also reviewed the evidence published about this topic.

CASE REPORT

1st pregnancy (2016): 31-year-old patient, primiparous, referred to the Son Espases hospital at week 32.5 of gestation due to rapidly evolving **ventriculomegaly**. She had no medical problems and a normal course of the pregnancy until then.
The ultrasound revealed **severe ventriculomegaly**, especially at the posterior horns of lateral ventricles. It also showed an hyperechogenic image at left choroid plexus, thus suspecting hemorrhagic etiology.
MRI reported post-hemorrhagic hydrocephalus secondary to **intraventricular germinal matrix bleeding**, probably associated with **hemorrhagic infarction (grade IV)**. A priori, etiological study, including genetics, was normal.

2nd pregnancy (2018): This pregnancy had a closer control because of the precedent. During the follow up, at week 26.6 of gestation, dilatation of the anterior horns of lateral ventricles was found, associated to a slightly irregular morphology, as well as **hyperechogenic nodular formations** on the inner edge. No other findings of interest.
MRI at week 30.5 reported a **bilateral frontal ventriculomegaly** with white matter reduction. In the following ultrasounds, the ventriculomegaly got worse, eventually associating as well hemorrhagic infarction (grade IV).

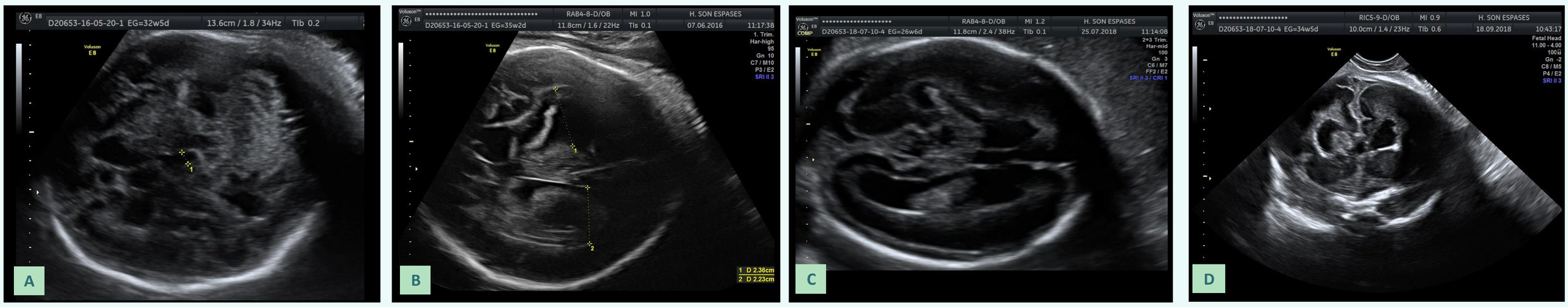

Figure 1 – Fetal Ultrasound. A: 1rst pregnancy 32.5w, axial section shows dilatation of lateral and third ventricle. **B:** 1st pregnancy 35.2w severe ventriculomegaly and hemorraghic infarction. **C:** 2nd pregnancy, 26.6w. It shows irregular morphology of lateral ventricles with hyperechogenic nodular formations at their walls. **D**: 2n pregnancy, 34.5w. Transvaginal coronal section shows anterior horns of the lateral ventricles and third ventricle dilatated. It also shows blood clots inside.

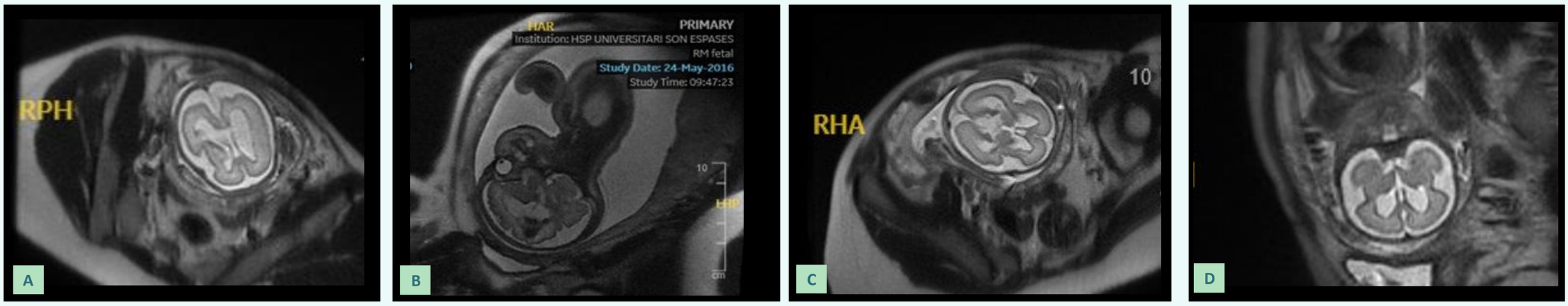

Figure 2 – Fetal MRI. A, B: 1st pregnancy, 34w. At parietal lobe we can see intraparenchimal damage. Posthemorrhage hydrocephalus secondary to intraventricular germinal matrix bleeding, associated to hemorrhagic infarction (grade IV). **C, D:** 2nd pregnancy, 30.5w. Frontal horns of the lateral ventricles are dilatated, with thinning of white matter.

Postnatally, both siblings suffered from **infantile cerebral palsy with spastic quadriplegia** caused by severe prenatal brain hemorrhages. The first child died at 5 years old due to an acute respiratory process.
Genetic study with exomes targeting IVH were normal in both siblings. **Study of homozygosity** between the two siblings found a **pathological loss-of-function variant in the ESAM gene**, which encodes for a protein related to endothelial adhesion molecules and the structure of the BBB. Parents and both grandmothers were heterozygous for the same variant. This new variant is related to a group of diseases that are recently described as **"thightjunctionopathies"**.

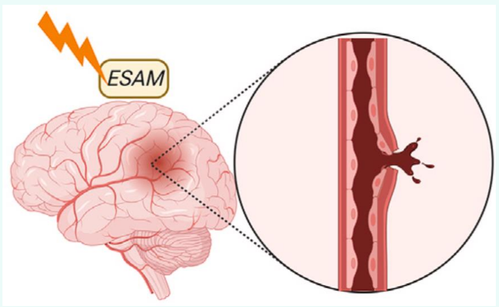

Image from Lecca et al. 2023

CONCLUSIONS

- Fetal intraventricular hemorrhage is an important cause of infant morbidity and mortality.
- IVH results from the bleeding of the germinal matrix.
- We have to think of this disorder when ultrasound findings are ventricular dilatation and/or intraventricular hyperechogenic masses (blood clots).
- When the cause is not identified, a genetic disorder must be studied.
- The identification of IVH genetic causes can guide the counselling process with respect to the recurrence risk and future pregnancies management.

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