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FETAL INTRAVENTRICULAR HAEMORRHAGE: DIFFERENT APPROACHES NEEDED? INSIGHTS ON GASLINI'S EXPERIENCE

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INTRODUCTION

The same brain lesion can show different aspects, complications and prognostic features at different ages. This is true also within the population of newborn babies in which an intraventricular haemorrhage can derive from a bleed of the germinal matrix in the most premature babies (GMH-IVH) compared to less premature or term babies presenting with choroid plexus haemorrhage. The severity and the number of complications are also affected by gestational age factors but the intrinsic vulnerability of the maturing brain due to the organ immaturity can also play a role during intrauterine life. Little is known about the less frequent intraventricular haemorrhage originating from the germinal matrix during fetal life. The aim of this retrospective analysis is to highlight characteristics of fetal GMH-IVH.

INCIDENCE

Fetal GMH-IVH has a much lower incidence than the postnatal form although its importance has been increasing in the last decade due to the growing number of prenatal diagnoses performed [1]

GMH-IVH with no-doubt is the most common type of fetal intracranial haemorrhage with an estimated incidence of 0.5–0.9/1000 pregnancies depending on sources considered [1 – 8] although many bias may make a trustable incidence a very difficult task.

Among these factors, minor forms escaping diagnosis, the confounding factors of mildly dilated ventricles, the lack of national registries and the possible termination of pregnancies. [1]

Postnatal GMH-IVH has overall incidence of about 20-25% among very low birth weight (VLBW) preterm babies, which decrease with increasing of gestational age. [9 - 15]

POSTNATAL AND PRENATAL PATHOGENESIS

Defining the pathogenesis of fetal GMH-IVH is extremely complex: an antenatal haemorrhagic lesion is usually an accidental finding highlighted during routine fetal ultrasounds. Establish the precise onset of intraventricular bleeding and triggering causes is extremely challenging. [1]

Furthermore, due to the low incidence of the disease and the extreme randomness and difficulty in diagnosis, controlled studies investigating potential risk factors are not currently available. Almost all currently known risk factors for GMH-IVH belong to the extrauterine environment and its effect on the immature brain. [9 - 15]

However, studying fetal GMH-IVH provides an unique opportunity to better understand the pathophysiology of postnatal GMH-IVH free from the stressors imposed by preterm delivery. Moreover, fetal GMH-IVH in term infants is also an opportunity to better understand outcomes after fetal GMH-IVH regardless of the risks associated with preterm birth. [1]

Postnatal GMH-IVH development depends on a complex interaction between anatomical, environmental and genetic factors [16 - 18], as well as placental pathology. [19]

Gestational age represents the most important risk factor for postnatal GMH-IVH. The occurrence of GMH-IVH is inversely proportional to gestational age: in infants born at 24 weeks of gestation, incidence of the most severe lesions ranges between 10 and 25%, while in surviving infants born beyond 28 weeks, such severe injury is diagnosed in <5% of cases. [9 - 15]

GMH-IVH is rarely observed beyond 32 weeks gestation: in late-onset cases, it is an epiphenomenon of other diseases like venous thrombosis. [9, 16, 20, 21]

GMH-IVH usually develops within the first week of life, mostly during the first 48/72 hours of life. In at least 50% of affected infants, GMH-IVH onset occurs on the first day of life, and by 72 hours around 90% of the lesions are identified. Progression to higher grades occurs rapidly, usually within 1 to 3 days. [12]

Germinal matrix is a highly vascularized region underneath the lateral ventricles of the developing brain. Its size has an incremental thickness until the 25th week of gestation, with subsequent progressive regression. [22]

Important factors involved in GMH-IVH genesis are represented by the intrinsic fragility of the germinal matrix microvasculature due to the immaturity of the vessel wall, fluctuations in cerebral blood flow and lack of autoregulation of cerebral blood flow. [22, 23]

Changes in venous pressure [22 - 25] and vascular anatomy are also part of this complex interaction. [17, 26, 27]

After the first week of life premature infants, even of extremely low gestational age, become relatively immune to intraventricular haemorrhage. [28]

The underlying reason seems to be related to the increase of oxygen concentration in blood and tissues after birth, which suppresses the production of specific growth factors (VEGF, angiopoietin-2), resulting in a blockage of the angiogenesis process and a concomitant maturation of blood vessels, which would therefore become more resistant at the break or simply making the anatomical involution of germinal matrix faster due to oxidative stress. [22, 29]. These potential mechanisms are very unlikely to occur during intrauterine life.

As largely demonstrated in several case studies and scientific papers, administration of prenatal steroids seems to be associated with a so drastic reduction in the incidence of GMH-IVH that it is considered the most reliable prophylaxis to reduce its incidence. [30 - 32]

Causal factors implicated in the genesis of fetal GMH-IVH are still unknown, but gestational age and environmental factors could be excluded. The most accredited hypotheses about causal factors are linked to genetic and anatomical factors, without forgetting the placental pathology. [16, 17, 19, 33, 34]

Due to early onset of GMH-IVH during fetal life, it is plausible that uterine environment and particularly placenta influence its development. Macroscopic and histological characteristics of the placenta reflect the intrauterine quality of life. Our group demonstrated an association between placental lesions and risk of developing postnatal haemorrhagic brain lesions. Similarly, in the prenatal period, the placenta could play a role in the regulation of cerebral blood flow and in the onset of GMH-IVH. [19]

A causal link between GMH-IVH onset and venous anatomical factors , for example the morphology of the subependymal veins (SV), was formulated by Larroche in 1964 [35] and emphasized up by Volpe [12].

Recently our group demonstrated a positive correlation between the presence of SV anatomical variants and GMH-IVH onset in preterm infants: a peculiar venous drainage may increase the risk of developing venous stasis e venous thrombosis, both known risk factors for GMH-IVH. [17]

Hypotheses about an association with genetic alterations responsible for thrombophilia or other coagulation disorders, such as alterations of factor V Leiden [16, 36, 37] or collagen proteins alteration [38], have been stated.

The link between thrombophilia and GMH-IVH pathogenesis is uncertain although qualitative and quantitative abnormalities in coagulation and fibrinolysis have received increasing attention as predisposing factors. The role of genetic polymorphisms involved in

the coagulation pathway in the development of GMH- IVH is probably a consequence of an increased risk of thrombosis in the fine blood vessels within the germinal matrix. [36, 39]

Factor V Leiden mutation, a well-known prothrombotic polymorphism, seems to increase the risk of developing GMH-IVH, although it may protect carriers from developing the most severe forms [36].

Type-IV collagens are proteins of the basal membrane and are expressed in all tissues, including vessel walls. Type IV collagen a1 (COL4A1) and type IV collagen a2 (COL4A2) chains, in particular, form the principal component of vasculature, renal and ocular basement membranes. They ensure the maintenance of vascular tone and endothelial integrity. Mutations of these genes have been associated with a wide spectrum of anomalies, in particular of the brain. Mutations in COL4A1 gene are well related with cerebral microangiopathy, familial porencephaly, aneurysms, ocular manifestations, nephropathy [38, 40] and fetal intracranial haemorrhage. [41]

Mutations in COL4A2 gene have also been reported to result in both sporadic and familial porencephaly. Several isolated cases of prenatal cerebral damage related to COL4A1 and COL4A2 mutations have been reported in fetuses and neonates. [38 - 41]

MTHFR is an enzyme that catalyzes the reduction of 5,10- methylenetetrahydrofolate to 5-ethyltetrahydrofolate, a substrate in remethylation of homocysteine to methionine. Polymorphism of MTHFR gene result in increased blood plasma homocysteine concentration. Hyperhomocysteinemia may lead to injury of vascular endothelium and lead to stroke, thrombosis, migraine and vascular disorder. It is described that MTHFR 1298A>C polymorphism is more prevalent in cases of IVH [42]

DIAGNOSIS

Prenatal diagnosis of fetal GMH-IVH is usually performed by both ultrasonography and subsequently magnetic resonance imaging. Obviously, the characteristics of MRI are more suitable for finding even the smallest lesions or structural alteration consequent to previous injury. On the other hand, this type of radiological examination is limited to second-level diagnosis originally discovered or suspected by ultrasound scan.

With advances in antenatal ultrasound, fetal GMH-IVH has been increasingly recognized. A cranial ultrasound on admission allows pre-existing antenatal brain injury to be identified. If antenatal GMH-IVH occurred well before birth, residual findings (ventricular dilatation, intraventricular clots and strands, parenchymal defects) may be.

Volpe's grading system of GMH-IVH severity [12], adapted by the original Papile classification [28] is therefore useful for fetal GMH-IVH. The problem is further compounded by the fact that not rarely the diagnosis is made when the complication of post-haemorrhagic dilatation is evident.

ASSESSING THE DEGREE OF SEVERITY

The grading system most commonly used for GMH-IVH in the infant was first reported by Papile in 1978 [28]. It has been used for decades and is still suitable to describe both early and late cranial ultrasound haemorrhagic appearances. This classification is based on the presence and amount of blood in the germinal matrix and the lateral ventricles. Initially this classification was developed for computer tomography scanning, but is now commonly used for any form of neuroimaging.

Grade I represents haemorrhage confined to the subependymal germinal matrix, grade II has haemorrhage within the lateral ventricles without ventricular dilatation, grade III IVH has haemorrhage with distention resulting in ventricular dilatation and/or haemorrhage occupying more than 50% of the ventricle, and grade IV IVH has parenchymal haemorrhage.

The adapted classification of Volpe [12] recognize three different degrees of GMH-IVH (grades I, II and III of Papile classification): the presence of periventricular haemorrhagic infarction lesions is noted separately because these abnormalities generally are not caused simply by extension of GMH-IVH into normal brain parenchyma, but GMH-IVH itself leads to obstruction of the terminal veins and impaired blood flow in the medullary veins with the occurrence of haemorrhagic venous infarction.

Although grade IV IVH is a periventricular haemorrhagic infarction rather than an extension of IVH per se, most reports continue to classify the cranial ultrasound findings according to the earlier Papile classification system and use the term grade IV IVH for this severe lesion.

Papile criteria	Description	Volpe criteria	Description
Grade I	Haemorrhage limited to germinal matrix	Grade I	Blood in the germinal matrix with or without IVH less than 10% of ventricular space
Grade II	Blood noted within the ventricular system but not distending it	Grade II	IVH occupying 10–50% of ventricular space on parasagittal view
Grade III	Blood in the ventricles with distension of the ventricles	Grade III	IVH occupying greater than 50% of ventricle with or without ventricular echo-densities
Grade IV	Intraventricular Haemorrhage with parenchymal extension	Separate notation of other findings	Periventricular Haemorrhagic infarction

Table 1. Papile and Volpe Grading Systems

As evidenced by previous works [1 - 6], complications such as PHI and PHVD are very often associated with fetal GMH-IVH. PVHD is diagnosed as a GMH-IVH-associated ventricular dilatation.

Fetal cerebral dilatation, also defined as ventriculomegaly, is usually defined as a lateral ventricle (LV) atrial diameter of >10 mm on prenatal ultrasound in the second and third trimesters of pregnancy. The atrium of the LV is the part at which the body, posterior horn, and temporal horn converge. Prenatally detected fetal ventriculomegaly is divided in two categories: mild (10-15 mm) or severe (>15 mm). [43]

The terms hydrocephalus and ventriculomegaly are often used interchangeably. A more accurate definition discriminate between hydrocephalus (used to describe pathologic dilation of the brain’s ventricular system due to increased cerebrospinal fluid pressure, usually as a result of obstruction) and ventriculomegaly (a mild enlargement form nonobstructive causes). [43]

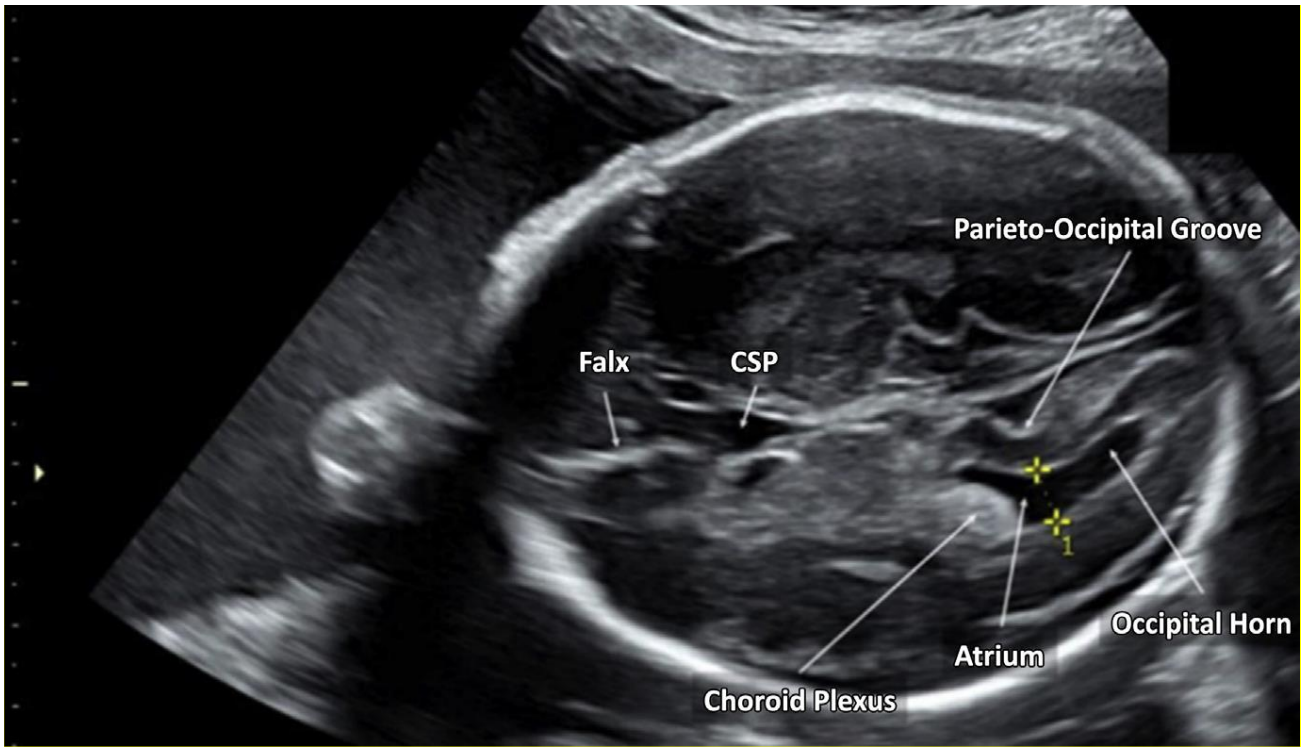


Figura 1. Appropriate measurement of the lateral cerebral ventricle (Courtesy of SMFM)

The importance of a correct measurement of the LV is crucial, because even a small difference can result in false-positive or false-negative results. The atrium of the LV should be measured in the axial plane at the level demonstrating the frontal horns and cavum septi pellucidi (CSP), in which the cerebral hemispheres are symmetrical in appearance.

The atrial diameter remains stable between 15 and 40 weeks of gestation, and ventriculomegaly generally cannot be diagnosed before 15 weeks of gestation. When the lateral ventricle is dilated, the choroid plexus falls toward the dependent ventricular wall and is referred to as a “dangling choroid.” The choroid will generally take up less than one-half of the CSF space when the ventricle is dilated. [43]

COMPLICATIONS

Although etiopathogenesis of fetal and postnatal GMH-IVH seems to be quite different, major complications are similar: periventricular haemorrhagic infarction (PHI) and post-haemorrhagic ventricular dilatation (PHVD). [9 - 12]

A major problem is about the treatment of these forms, first of all post-hemorrhagic hydrocephalus. Surgical treatment necessary to solve the ventricular size increase must necessarily perform out after delivery.

Early recognition of the pathology becomes essential to allow an adequate control of lesion progression. In such cases remains of paramount importance to discriminate the timing for surgical intervention, not rarely anticipating the time of birth.

The balance to decide when to deliver the baby in order to offer the best timing for surgical intervention counterbalanced by the risk of delivering a baby too soon should be based on evidence based indications for surgery that even in the postnatal cases are not often so adopted by all centers.

PERIVENTRICULAR HAEMORRHAGIC INFARCTION

PHI complicates GMH-IVH in about 15% of cases. GMH-IVH of all grades can be complicated by PHI, but the higher the grade of GMH-IVH, the more probable PHI occurs. [10]

PHI is caused by venous obstruction induced by GMH-IVH. Venous congestion leads to ischemia and to secondary haemorrhagic infarction. High intraventricular pressure due to a large haemorrhage may affects flow through the subependymal veins, increasing infarct size. Cerebral palsy and severe cognitive impairment are common in infants who suffered from PHI. Prognosis is highly dependent on location and extension [10, 12]

PHI ultrasound appearance is a characteristic triangular, “fan-shaped” echodensity in periventricular white matter, ipsilateral to GMH-IVH. In the first phase the lesion appears separated to the ventricle wall, but later it may subsequently grow until touching the ventricle wall and eventually merge into a single, large hyperechoic lesion together with the initial GMH-IVH. [12, 44, 45]

After few days from its appearance, the parenchymal hyperechoic area starts to decrease, pointing out the venous congestion resolution of the area surrounding the infarction, which may lead clinicians to overestimate the extent of PHI during the acute phase. PHI often remains separate from the initial GMH, appearing as a small hyperechoic lesion in ipsilateral periventricular white matter. Multiple minute PHIs along the course of the medullary veins can also be observed. [10, 45, 46]

Minor PHIs may result from partial obstruction but not occlusion due to compression of a subependymal collector vein by the GMH. The risk of developing PHI following a

subependymal GMH might be related to the location of the GMH itself, especially in association with a peculiar venous anatomy prone to congestion, for example, the presence of acute venous angles. [26, 47]

PHI usually evolves into cavitation within periventricular white matter. As most PHIs develop adjacent to the ventricular wall, porencephaly resulting from the cavitation is common after 1 or 2 months. Regardless of the evolution into porencephaly, a cavitation resulting from PHI is usually single, asymmetric and persistent. Conversely, cysts of periventricular leukomalacia typically show a symmetrical, mainly posterior distribution and tend to disappear within few weeks, insomuch that they are often undetectable at term-equivalent age. [12, 46, 47]

Classifying PHI into venous subtypes helps to predict outcome and counsel parents in this difficult situation, and this should be expanded in relation to specific behavioral or cognitive sequelae. [26, 47]

Dudink [47] classified PHI into venous subtypes and showed how their classification correlates with motor outcome. Advanced MRI techniques like DTI (diffusion tensor imaging) add useful information for prediction of outcome. Mortality in infants with extensive PHI is high, especially when it occurs bilaterally. [9 - 12]

In many countries, redirection of care and end of life decisions are considered in infants with bilateral PHI. Although robust data on this are lacking, it is certain that redirection of care contributes significantly to reported mortality rates. [9 - 12]

PHI with an atypical time of onset (antenatal or after 96 postnatal hours when unrelated to a clinical deterioration) has been associated with the presence of thrombophilic disorders, especially factor V Leiden. [16]

POST HAEMORRHAGIC VENTRICULAR DILATATION

The term PHVD refers to dilatation of the ventricles subsequent to GMH-IVH. Approximately 25% of infants with GMH-IVH develop progressive PHVD. [12]

The risk of PHVD is higher following severe GMH-IVH, but it may complicate each grade, even isolated GMH. The vast majority of instances of progressive PHVD (80%) follow IVH III, often in combination with a PHI. [12]

PHVD is related to an imbalance between production and circulation and/or resorption of cerebrospinal fluid. It usually develops between few days to few weeks after the initial GMH-IVH. Obstruction to cerebrospinal fluid circulation by clots or fibrin debris contribute to ventricular enlargement. Most often it follows obstruction of liquor pathways around the cerebellum. [12]

The patient can develop various types of ventricular dilatation according to the location of the obstruction, from unilateral type following unilateral obstruction at the foramen of Monroe even to tetraventricular hydrocephalus following obstruction of the fourth ventricle outlets. [12]

While in most cases PHVD eventually resolves (40% spontaneously and another 15% after nonsurgical treatment), around 35% of infants with progressive PHVD require surgical treatment, while 10% die [48, 49].

Diagnosis and evaluation of PHVD is usually made with cranial ultrasound, which is obviously more reliable than clinical assessment (anterior fontanel tension, head circumference or sunset phenomena of the eyes). [50]

The widely used measure is the ventricular index (VI) of the lateral ventricles measured on coronal section (the distance between the falx and the lateral wall of the anterior horn in the coronal plane at the level of the third ventricle), introduced by Levene in 1981 [51], who demonstrate the very close correlation between measurement of ventricular size made on coronal section and the ventricular index. Levene was also able to demonstrate that the upper limit for the VI depends on gestational age. Levene's nomogram is still used today to compare VI measurements and to differentiate what is pathological from what is not.
The limitation of using only VI to assess ventricular enlargement is that often VI starts to increase in a more severe hydrocephalus, failing to identify neonates with mild dilatation [50 - 52].

The first sign of a ventricular dilatation is usually a ventricular shape change, with the rounding of the frontal horns (ballooning) and an increase in anterior horn width (AHW). AHW (defined as the diagonal width of the anterior horn measured at its widest point in the coronal plane) has been suggested to be a more sensitive marker for early or mild ventricular enlargement than the VI. [52]
Differently from VI, AHW does not correlate with GA. Usually a value less than 3 mm is considered normal, instead of values exceeding 6 mm are associated with ventricular ballooning and suggest the need for treatment. [44, 50 - 52]

Assessment of ventricular dimension and enlargement could be made also in sagittal scans, by measuring the depth of the occipital horn of the lateral ventricle (the distance between the outermost point of the thalamus at its junction with the choroid plexus and the outermost part of the occipital horn in the parasagittal plane), which is called thalamo-occipital distance (TOD). Occipital horn size is often earlier visible than the increase in the size of the frontal

horn. Furthermore, the occipital horn is generally more dilated than the frontal horn and may be the only site of ventricular dilatation. [26, 50 - 52]

After years of controversy, in 2012 Brouwer [53] demonstrated that TOD is related to GA and provided reference values and a nomogram that can be used to compare the measurements obtained in clinical practice.

The clinical value of measurements of the third and fourth ventricle is unclear: assessment of the size of the third and fourth ventricle size may help in differentiating between communicating and non-communicating hydrocephalus, or to distinguishing PHVD from ex-vacuo dilatation. The observation of isolated dilatation of the third or fourth ventricle can be associated with posterior fossa haemorrhage and may conduct to the proper diagnosis. [50 - 52]

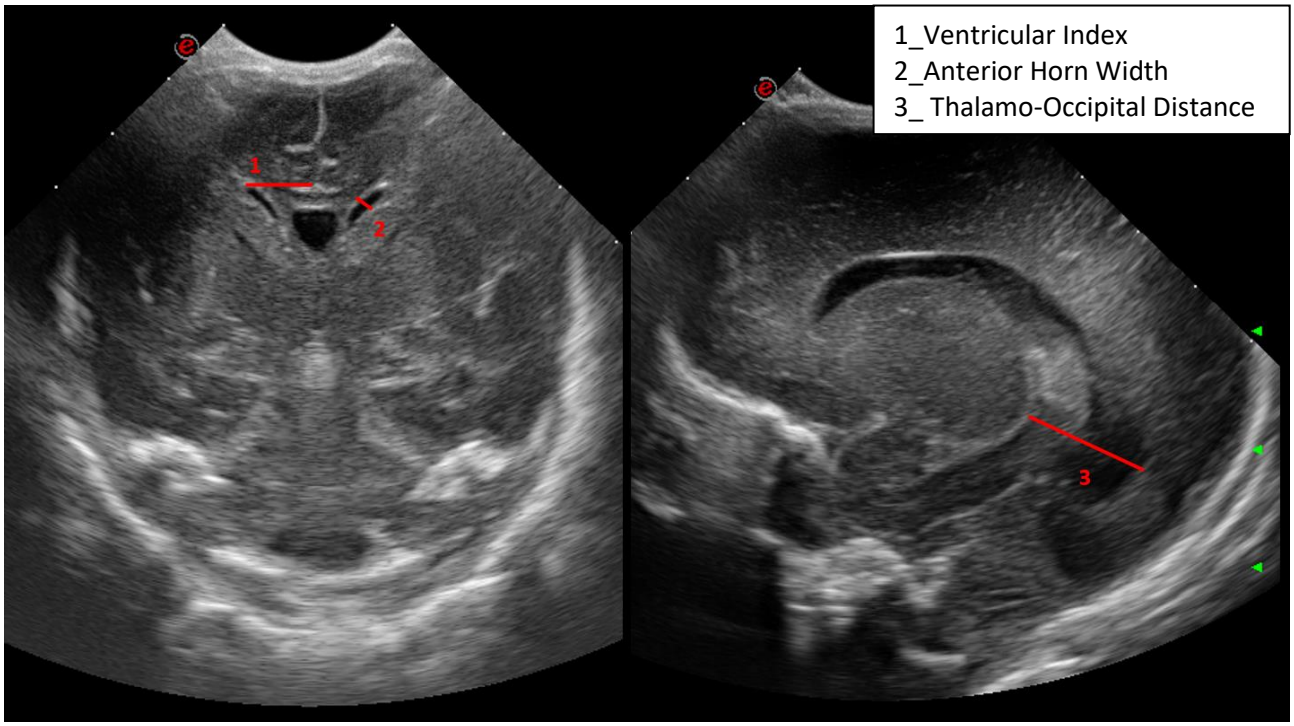


Figure 1. PHVD ultrasound normal measurement.

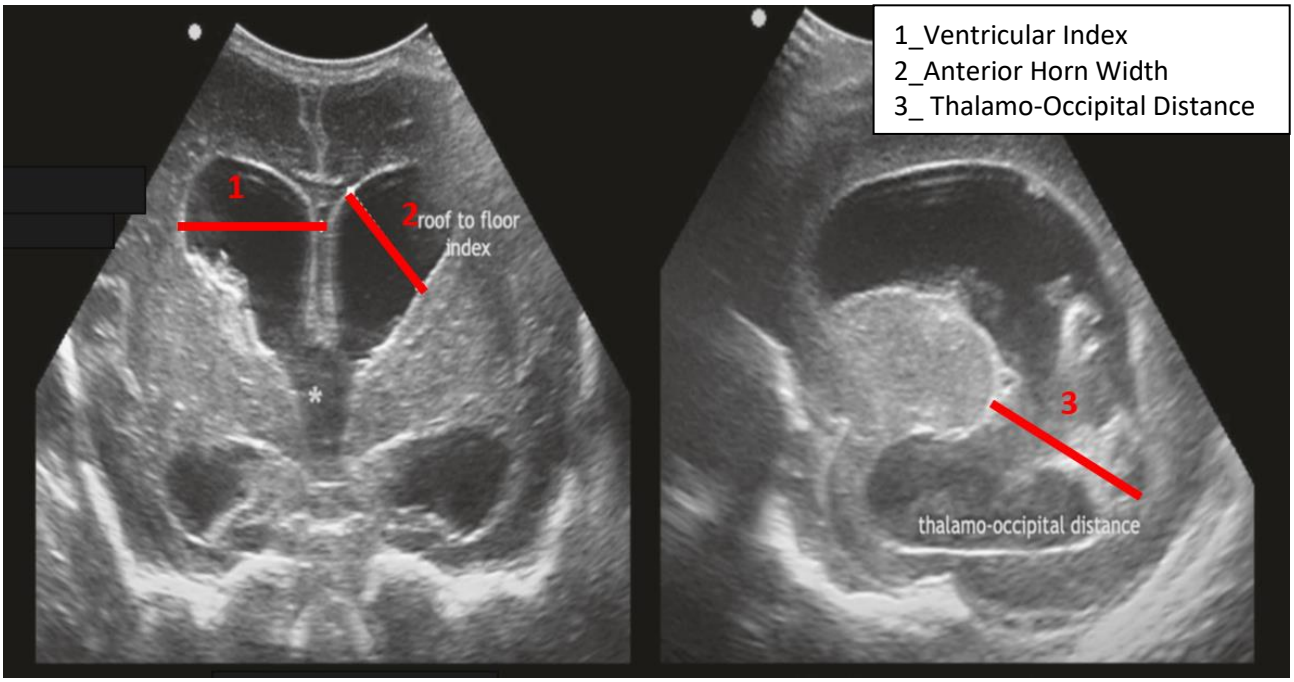


Figure 3.PHVD pathological measurement (Courtesy of Parodi et al)

Despite decades of extensive research, treatment of PHVD remains challenging. No international consensus exists on optimal timing, but the majority of European Centers initiate treatment once the ventricular width has crossed the 97th percentile + 4 mm line on Levene's graph [53 - 55].

On the other hand, several treatment options were investigated: lumbar or ventricular tapping, cerebrospinal fluid (CSF) drainage and fibrinolytic treatment, endoscopic third ventriculostomy (ETV), surgical insertion of an external drainage (EVD), a subcutaneous reservoir and permanent ventriculo-peritoneal shunting (VPS) [48, 49, 54, 55].

At our institution, the Pediatric Neurosurgical Unit considers EVD as the first choice treatment for very low- birth-weight infants with posthemorrhagic hydrocephalus. Our neurosurgeons has a great experience with this device, performing nearly 20 interventions for year [48, 49, 56 - 58] and experimenting new techniques to reduce risk factors and complications of surgical interventions [59].

However, the key problem is to balance between the adverse effects of PHVD on the immature brain and the risk of complications of interventions.

As well as most surgical treatments, those designed to resolve PVHD are not free from complications. Even the placement of an EVD, which can be understood as a temporary and therefore less invasive treatment, must be managed by expert personnel to avoid sometimes fatal complications.

The main risks are related to infection and pull-out of the device. A pull-out usually needs another surgery to replace the catheter, causing additional operative costs and even

additional morbidity (EVD replacement elevates the risk of infection up to 29% when compared with 6% risk of patients who had no replacement) as well as a significant risk of severe complications resulting from raised intracranial pressure. [59]

OUTCOMES

Even if causal factors involved in the development of fetal disease are still unclear, outcomes and consequences are better known and their management is similar to preterm babies with postnatal development of GMH-IVH. PHVD is strongly associated with neurodevelopmental impairment, particularly in infants with persistent PHVD that requires surgical intervention and if PHVD is combined with PHI. [10, 12, 48]

PVHD is strongly associated with motor impairment, neurodevelopmental challenges, and epilepsy, similar to preterm infants. However, the relationship between severity and short- and long-term outcome of antenatally diagnosed GMH-IVH is not known though small studies suggest one may exist. [1 - 8]

Children with PHI had higher odds of epilepsy and developmental delay compared to children without a history of antenatal parenchymal injury (epilepsy: OR 8.55, 95% CI 2.12–48.79, $p<0.001$; developmental delay: OR 6.46, 95% CI 2.64–16.06, $p<0.001$). [1]

AIM

This study aims to describe the characteristics of a cohort of infants admitted to the Neonatal Intensive Care Unit department (NICU) of “Gaslini Children’s Hospital” who developed antenatal GMH-IVH before birth and their clinical and neurosurgical outcomes.

Moreover, our purpose is to define a useful parameter to diagnose a ventricular dilatation worthy of neurosurgical treatment, by comparing prenatal and postnatal methods for diagnosing of cerebral ventricular dilatation in utero.

METHOD

This is a retrospective monocentric study. From April 2012 and September 2022 a total of 1802 term and preterm infants admitted to our NICU department underwent cerebral magnetic resonance (MRI).

Among them, we carefully chose all patients with a GMH-IVH diagnosis made by MRI after birth. After that, we examined clinical histories of the patients and we included only them who had a diagnosis of GMH-IVH made by ultrasound scans or MRI during fetal life.

Exclusion criteria were cerebral lesion related to an antenatal infection (for example cytomegalovirus infection), metabolic disease, arteriosus-venous malformation, perinatal stroke.

For each patient we collected information about the pregnancy (maternal diseases, antenatal ultrasound and MRI findings, gestational age at diagnosis of fetal GMH-IVH) and about the infant (type of delivery, need for resuscitation, gestational age and weight at birth, clinical course).

We therefore highlight need for neurosurgical treatment, the type of surgery performed and the treatment outcomes. In case of failure we also noted the subsequent surgical treatments and their effectiveness. Finally we collected data on the neurocognitive development and psychomotor retardation of patients affected by fetal GMH-IVH, both undergoing surgery and untreated, which were followed by our neonatal follow-up.

Our internal ultrasound monitoring protocol was introduced in 2012 and it provide a close program of ultrasound scans for term and preterm babies admitted In our NICU.
Due to our protocol, a strict ultrasound monitoring was performed in all the infants affected by GMH-IVH, included them with antenatal onset type.

The severity of GMH-IVH was graded according to Volpe [12].
Ventricular dilatation was defined as a VI > 97th percentile for gestational age, according to Levene [51].

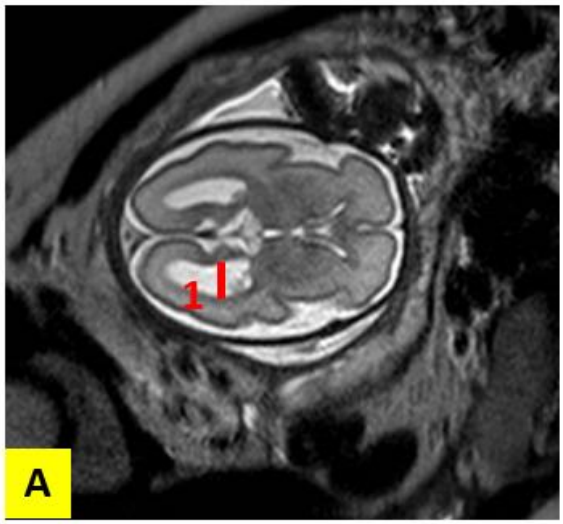
Pediatric neurosurgical unit of Gaslini Children Hospital, has long-standing experience with external ventricular drainage (EVD) as a temporary measure for hydrocephalus and performs nearly 20 interventions every year, both in children and in preterm infants, [56 - 59] and this is the first choice in the treatment of infants with post-haemorrhagic hydrocephalus.

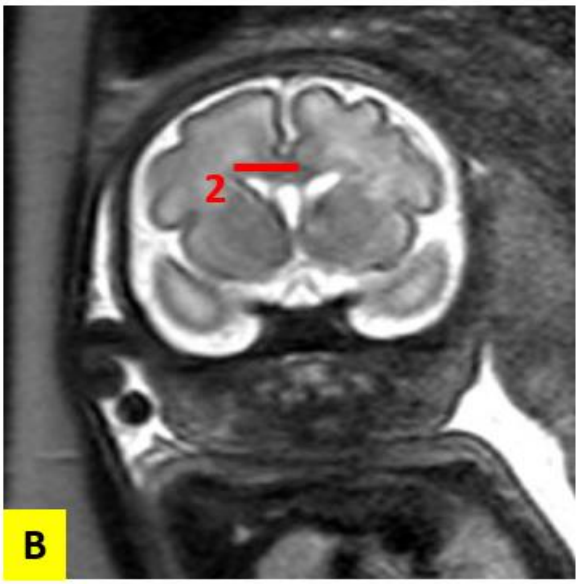
Both symptomatic and asymptomatic infants with a VI 4 millimeters wider than the 97th percentile for GA (p97° + 4 mm), after brain MRI confirmation of the severity of the hydrocephalus, were promptly treated by placing a neurosurgical device (for example, EVD). The procedure was performed regardless of the infant's weight or postmenstrual age.

At the end of the data collection and analysis, we compared our data with preterm infants affected by post-natal onset GMH-IVH, from case histories already published by our group [48, 49].

To compare prenatal and postnatal ventricular dilatation measurements, we reviewed fetal and postnatal MRI of patients with fetal GMH-IVH.

In prenatal MRIs we measured the diameter of the atria of the lateral ventricles in the axial plane (LVAD) [43] and the ventricular index in the coronal plane at the level of the Monroe foramina. In the post-natal MRIs we instead measured only the ventricular index [51 - 53], using it as a key parameter for defining the need for neurosurgical treatment. [54]
(Figure 4 and 5)





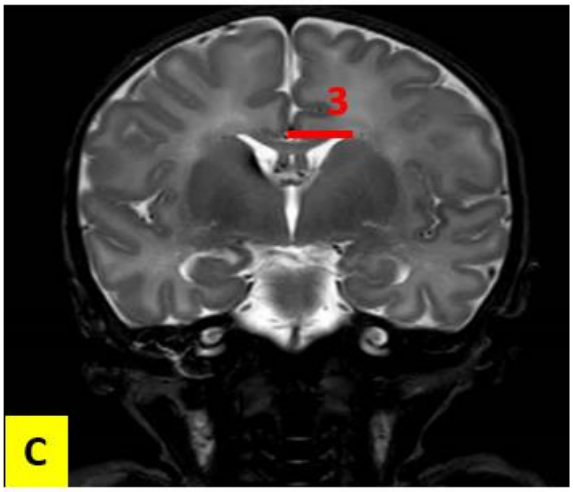
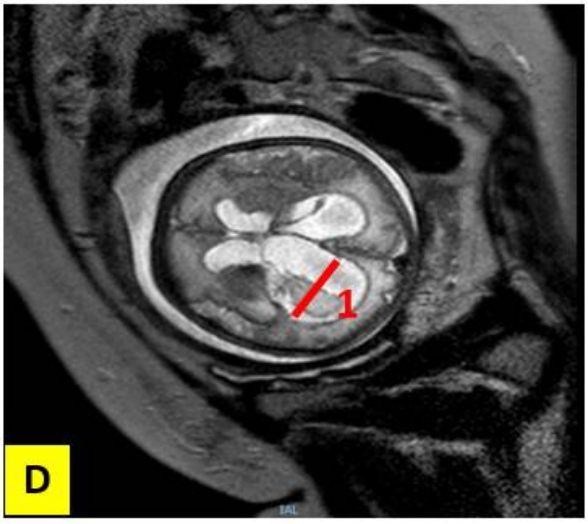
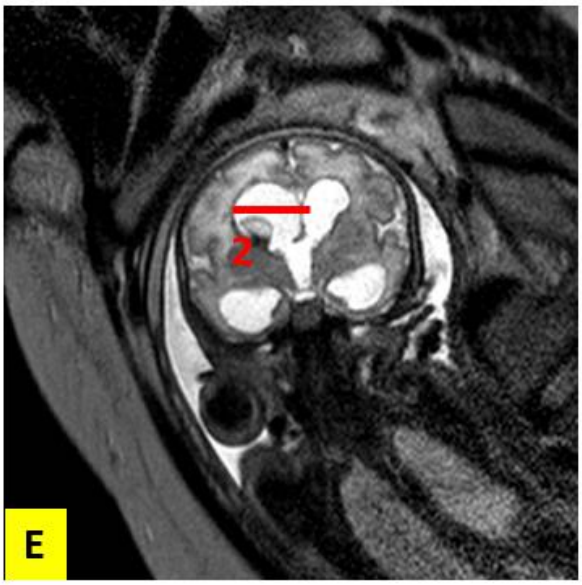


Figure 4. Prenatal and Postnatal Ventricular measurement in healthy infant





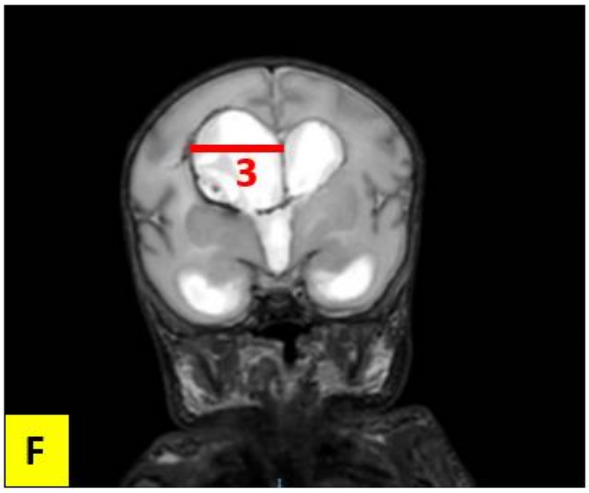


Figure 5. Prenatal and Postnatal Ventricular measurement in infant with ventricular dilatation

Legend
1_Lateral Ventricle Atrium Diameter
2_Prenatal Ventricular Index
3_ Post-Natal Ventricular Index

A, D_Fetal MRI, axial plan
B, E_Fetal MRI, coronal plan
C, F_Postnatal MRI, coronal plan

RESULTS

Our retrospective research identified 28 cases of antenatally detected GMH-IVH, both by ultrasound and later confirmed by fetal MRI.

In our cohort, male accounted for 20 out of 28 patients (71,4%). The median gestational age at diagnosis was 30 weeks, ranging from 21 to 36 weeks. Only in one case pregnancy was terminated. Of the 27 liveborn babies, 8 were born at term age and 19 were preterm babies.

Median gestational age at birth was 35 + 3 weeks, ranging from 27 + 2 and 40 + 1. Median birth weight was 2530 g. Only considering preterm babies (gestational age at birth lower than 37 weeks) median gestational age was 33 + 1 and median birth weight was 2320 g.

Excluding the only case of termination of pregnancy, mortality rate was 11,1% (3/27).
Two infants died after delivery due to preterm birth acute complications. One newborn died at 15 months of age after a new cerebral bleeding.

As reported in *Table 2*, Grade I/II Germinal Matrix haemorrhage – Intraventricular haemorrhage (defined as low grade GMH-IVH) was detected in 5 patients of 28 (17,8%), grade III in 7 patients (25%) and PHI in 16 of 28 cases (57,1%).

Post haemorrhagic ventricular dilatation occurred in 23 cases (82,1%), exclusively with high grade GMH-IVH (grade III GMH-IVH and/or PHI).

GMH-IVH was right-sided in 13 babies, left-sided in 7 babies, and bilateral in 8 cases.

GMH-IVH GRADE	1	2	3	PHI	TOTAL
TOTAL	2	3	7	16	**28**
RIGHT SIDE	2	1	3	7	**13**
LEFT SIDE	0	0	1	6	**7**
BILATERAL	0	2	3	3	**8**
HYDROCEPHALUS	0	0	7	16	**23**
TOTAL VD PLACED	0	0	4	9	**13**
EVD	0	0	4	2	**12**
VPS	0	0	1 (+2 ETV)	8	**9**
REMOVE	0	0	1	1	**2**
EPILEPSY	0	0	0	3	**3**
DEVELOPMENTAL DELAY	0	0	1	7	**8**

Table 2. Fetal GMH-IVH Features

Legend
ECD: external ventricular drainage
ETV: endoscopic third ventriculostomy
GMH-IVH: germinal matrix haemorrage - intraventricular haemorrhage
PHI: post-haemorrhagic ventricular infarction
VD: ventricular devices
VPS: ventriculo-peritoneal shunt

An associated condition was found in 11 cases: 3 patients were born from twin pregnancies, 4 babies had amniotic fluid abnormalities such as polyhydramnios, 2 of them had a cardiovascular malformation. One patient's mother was affected by MTFHR mutation.

Nine patients of 28 were investigate for factor II and factor V Leiden genetic mutation, but no one was found positive.

Epilepsy affected 3 of 22 (13,6%) cases where outcomes were adequately described. None of the cases with grade I, II or III GMH-IVH experienced seizures. Epilepsy was documented in 3 out of 11 (27,2%) of PHI cases.

Developmental delay was documented in 11 out of 21 (52,3%) cases with sufficient reporting of outcomes. Developmental delay was not described in any of the children with grade I/II GMH-IVH, regardless of gestational age at birth, and was present in 1 out of 5 (20%) children with grade III GMH-IVH, and 10 out of 11 (90,9%) children with PHI.

Of the 23 babies who developed post haemorrhagic ventricular dilatation, 7 were grade III IVH and 16 were PHI. No low grade GMH-IVH developed PHVD.

One of the 23 cases of PVHD undergone pregnancy interruption and 2 other babies died before surgical treatment.

Fourteen (70%) of the remaining 20 babies with PHVD underwent neurosurgical treatment for exceeding the p97 + 4 mm limit. The others six babies were discharged without neurosurgical treatment.

A temporary EVD was placed in 11 of 14 babies (78,5% of the PHVD treated cases, 47,8% of the total PVHD cases) to treat ventricular dilatation.

The other 3 babies underwent different treatment: an endoscopic third ventriculocisternostomy (ETV) was performed in one patient, another patient underwent a septostomy and the last one was treated with ventriculoperitoneal shunt (VPS) insertion, due to the prolonged dilatation of the ventricular system during fetal life. Median age at the surgery was 5,4 days.

Between the eleven patients treated with EVD placement, 7 needed afterwards a permanent VPS (63,6%) due to failure of the temporary device, one patient removed EVD definitely (9,1%) and ETV was performed in 3 cases (27,2%), allowing EVD removal.

The only baby who underwent septostomy did not require any further treatment.

Another patient, who was first treated with ETV, later needed positioning of VPS.

EVD was definitely removed in 4 cases.

Total number of permanent VPS placed was 9 (39,1% of total PVHD and 64,2% of the PVHD requiring treatment).

Data about infants who developed PVHD are summarized in *Table 3.*

	GMH-IVH GRADE	FIRST TREATMENT	VPS PLACEMENT	DEVICE REMOVAL
NOT TREATED	**PHI**	Pregnancy Interruption		
	PHI	Deceased		
	PHI	Deceased		
	3	0	0	-
	3	0	0	-
	PHI	0	0	-
	PHI	0	0	-
	PHI	0	0	-
	PHI	0	0	-
TREATED	**3**	EVD	0 (ETV)	1
	3	EVD	0	1
	3	SEPTOSTOMY	0	-
	3	EVD	1	0
	3	EVD	0 (ETV)	1
	PHI	EVD	1	0
	PHI	EVD	1	0
	PHI	EVD	1	0
	PHI	VPS	1	0
	PHI	EVD	1	0
	PHI	ETV	1	0
	PHI	EVD	1	0
	PHI	EVD	1	0
	PHI	EVD	0 (SEPTOSTOMY)	1

Table 3. Neurosurgical Outcomes Of fetal PVHD

Legend
ECD: external ventricular drainage
ETV: endoscopic third ventriculostomy
GMH-IVH: germinal matrix haemorrage - intraventricular haemorrhage
PHI: post-haemorrhagic ventricular infarction
VD: ventricular devices
VPS: ventriculo-peritoneal shunt

A comparison between the atrium diameter and measurement of ventricular index from prenatal and postnatal MRIs was made.

Our cohort included 28 patients.

Six patients were excluded because lack of MRI (prenatal imaging of one patient was not available; prenatal MRI was not performed in two cases due to diagnosis made with ultrasound; postnatal MRI was not performed in three patients due to early death).

Of the remaining 22, five patients had mild ventriculomegaly (<15 mm of LV atrium diameter), the other 17 had severe ventriculomegaly (>15 mm of LV atrium diameter).

VI measured after birth was higher than p97° + 4 mm in 13 patients and 9 patients has VI after birth under p97° + 4 mm.

VI size measured on prenatal MRI was higher than p97° + 4 mm in 14 patients and under p97° + 4 mm in 8 patients.

Twelve of 22 patients underwent neurosurgical treatment.

All twelve patients treated had a diagnosis of ventricular dilatation made on prenatal MRI using lateral ventricle atrium diameter (LVAD). This diagnosis was therefore confirmed by a 97p + 4 mm measurement of ventricular index performed on MRI after birth.

Ventricular index measured on prenatal MRI was also 97p + 4 mm in 11 of 12 cases.

Ten patients with ventricular dilatation were not treated: one of them had a wide dilatation of one lateral ventricle, which remained stable between the prenatal and postnatal MRI, so it was decided to not perform any treatment.

Five of ten not treated patients had mild ventriculomegaly at prenatal MRI and VI at both prenatal and postnatal MRI smaller than p97 + 4 mm.

Four of ten not treated patients with LVAD indicative of severe ventriculomegaly at prenatal MRI, had VI measures at postnatal MRI smaller than p97 + 4 mm, so they do not underwent treatment. VI measured on prenatal MRI in those patients was suggestive for treatment in only 2 of 4 patients.

We calculate Positive predictive value (PPV) and negative predictive value (NPV) in define ventricular dilatation worthy of treatment for LVAD, prenatal VI and postnatal VI.

PPV for LVAD was 70.59% (56.36% to 81.69%) and NPV was 100.00%.

PPV for prenatal VI was 78.57% (58.35% to 90.56%) and NPV was 87.50% (50.65% to 97.95%).

PPV for postnatal VI was 92.31% (65.15% to 98.72%) and NPV was NPV was 100.00%.

DISCUSSION

Antenatal GMH-IVH represents a rare but important cause of mortality and morbidity in term and preterm infants. Although the lower diffusion compared to its postnatal-onset counterpart, antenatal GMH-IVH represents often a very challenging disease: the casual discovery of its prenatal onset during routine pregnancy monitoring ultrasound scans, leaves physicians powerless to face the complications and outcomes of the disease and complicate the communication with the family in such a delicate moment.

Despite this, further investigation of the origins, causes and mechanisms of the onset of GMH-IVH during antenatal life, an early stage of life free from implications connected to the outside world, are fundamental to understand how the disease develop to try to reduce both the prenatal and postnatal GMH-IVH incidence.

In this retrospective report, we showed clinical data of patients with prenatal GMH-IVH who have been take in charge and treated by our Neonatal Intensive Care Unit in an eleven years period.

This is a heterogeneous cohort of patients from different parts of Italy and, to date, it is the largest cohort of patients from a single center ever reported in literature. Only Echalal et al. [5] reported a wider cohort, but patients came from different hospitals of Jerusalem.

According to available literature, [1 – 8] in our cohort low grade GMH-IVH (grade I-II) are remarkably rarer (17,8%) than high-grade antenatal GMH-IVH, (grade III IVH and PHI, 82,3% of total cases). The percentage of PHI reported in our cohort (57,1%) is the highest among the previously reported literature data, instead of PHVD percentage (82,3%), is quite similar to data from the available literature and review. [12]

We remain uncertain on the reasons causing the very high number of PHI in our population. A potential explanation may simply derives from the high competence of our Neuroradiologists in detecting this complication of GMH-IVH, not often well known and therefore diagnosed by other radiologists, mainly keen on adult pathologies.

Another possible explanation could be related to a selection bias: due to the intrinsic difficult in diagnosis, minor forms may remain undetected, and the high percentage of PHI could be coincidental.

However, we speculated that those finding could be likely related to the fact that several patients are referred to our center at an already advanced stage of the ventricular dilatation from other centers across Italy, due to our widely recognized experience in preterm babies neurological field, as well as to perform a neurosurgical evaluation early after birth, in order to define the need for a surgical treatment.

As declared before, Pediatric Neurosurgical Unit of Gaslini Children Hospital has long-standing experience in post-haemorrhagic hydrocephalus surgical treatment, by performing almost 20 interventions every year, both in children and in preterm infants, [56 - 59].

However, our retrospective analysis revealed several interesting findings that need to be highlighted.

COMPARISON BETWEEN FETAL AND POSTNATAL GMH-IVH AND PHVD

One of the major problems remains the method of assessing the severity of post-haemorrhagic hydrocephalus. Measurements of lateral ventricles dilatation are totally different between prenatal approach in the fetuses and the postnatal one based on ultrasound via trasfontanellar window. The lateral ventricles are measured In the prenatal life looking at axial cut of the brain and viewing the entire lateral ventricles while the dilatation is measured at the atrium-trigonus (see figure 1). On the contrary the most diffuse technique in neonates is via anterior pseudocoronal cut assessing the dilatation of frontal horns (Levene technique, Figure 2 and 3).

These considerations make difficult to compare decisions for neurosurgical treatment and they may not help to understand why neurosurgical outcome of the newborns treated for PVHD is so different when we look at positioning of VPS.

Patients with prenatal GMH-IVH who developed PHVD needed more frequently a permanent VPS after failure of the initial treatment with EVD, compared to those described in our postnatal PHVD population by De Angelis et al (63,6% vs. 54%) [48].

That means that many preterm babies with PHVD manage to avoid VPS while this is not the same for fetal infants with PHVD.

The most convincing explanation is that when PVHD is diagnosed antenatally, lesion's onset and evolution are usually a late finding of a progressive severe ventricular dilatation.

The consequence is a delayed treatment with insertion of a temporary shunt and subsequent failure, which results in a major needs of VPS placement. Conversely, the development of PHVD after postnatal GMH-IVH could be better monitored with cranial ultrasound and promptly well managed with a temporary drainage to avoid the necessity of permanent shunt.

In other words, a delay in perform a neurosurgical intervention for PHVD is crucial for the success of the treatment.

According to this explanation Parodi et al [49] compare the incidence of permanent VPS placement between preterm born at Gaslini Hospital who developed PHVD in our NICU (inborn patients) and preterm born in another Italian center, subsequently transferred in our NICU after PHVD onset, to perform a neurosurgical treatment (outborn patients).

The author highlighted a higher percentage of PHVD needing VPS in the outborn patient group, (40% vs. 67%): a possible explanation to this is that outborn patients reached our hospital at a too advanced PHVD stage to be treated effectively with temporary EVD placement. Of note, we found similar percentage of fetal PVHD requiring permanent VPS (9 of 14, 64,2%).

We speculate that antenatal PHVD is usually a late finding of the pregnancy and cannot undergo an early management, similarly to PHVD developed in outborn patients, who reach our NICU in a late stage with a great dilatation.

Differently, patients who develop dilatation in a quarter-level NICU, where a close monitoring could be perform to define the best treatment timing, could have better chances to allow a VPS positioning.

However, the need of a prompt treatment for the progressive severe ventricle dilatation has to be balanced with the timing of delivery and the level of iatrogenic prematurity. In the absence of randomized trials, is particularly challenging, under the umbrella of neuroprotective strategies, reducing the potential damage of the progressive ventricular dilatation counterbalanced by the neurological risk of preterm birth due to an early iatrogenic delivery.

Another peculiarity that emerges from our data is the total absence of cerebellar bleeding in our cohort: no patient with fetal intraventricular haemorrhage was found having haemorrhagic lesions in the cerebellum (CBH). Our findings are consistent with those of Martino et al [60], who reported a case report of 17 patients with fetal CBH without associated fetal IVH.

Although predisposing factors for GMH-IVH and CBH on postnatal onset appear to be slightly different, the chance to have both lesions is high in preterm babies, as reported by Parodi et al [49].

Certainly the two cohorts reported by us and by Martino et al [60] are too small to exclude a correlation between the fetal onset of GMH-IVH and CBH, but they set up a starting point for future interesting studies

A NEW DIAGNOSTIC APPROACH FOR A BETTER DELIVERY TIMING CHOICE

Diagnosis of fetal GMH-IVH and PHVD is another challenging topic about this rare disease.

Scanning the brain of a fetus it is not equivalent to scan a preterm baby brain, not only for the technical difficulties of performing intrauterine US and MRI, but also for the different methods used for the measurement of cerebral ventricles.

In preterm newborn, neonatologists are used to measure the frontal horns dimensions with the widely accepted Ventricular Index parameter introduced by Levene [51], while obstetricians prefer to use the lateral ventricle atrium diameter for the in utero measurement of the cerebral ventricles [43], making more difficult a good comparison between prenatal and postnatal dilatation of ventricles.
Furthermore, colpocephaly (the selective dilatation of the posterior horns of the lateral ventricles) is common during fetal period and it could lead to less accurate measurement, especially for a millimetric mild increase.

The proposal of our study was to standardize prenatal and postnatal assessment of ventricular dilatation. Firstly we compare the accuracy of in utero and postnatal measures, LV atrium diameter (LVAD) and Ventricular Index (VI), in diagnosing a ventriculomegaly worthy of treatment.

For the analysis, we chose to match the MRI images rather ultrasound for two reasons: first, MRI is an operator-independent radiological exam; moreover, the decision to perform a neurosurgical treatment is usually made after execution of MRI.

Twelve of eighteen patients underwent neurosurgical treatment for suspect fetal ventricular dilatation confirmed after delivery by postnatal MRI.

Of the twelve treated patients, all of them had a LVAD >15mm, defined as severe in utero ventriculomegaly, and a postnatal VI higher than p97° + 4 mm, thus configuring the need for treatment according to the current clinical practice in force in our neurosurgery unit. Interestingly VI measured at the fetal MRI was p97° + 4 mm in 11 of 12 cases.

Ten patients were not treated.

One patient with significant ventriculomegaly was not treated despite the higher postnatal VI (p97° + 10 mm) due to the stability of the lesion during all the fetal life and after delivery.

Of the remaining patients, five of them did not have severe ventricular dilatation considering all measurement: LVAD, prenatal VI and postnatal VI.

The last four patients had a size of the LVAD >15 mm, that means severe ventricular dilatation, but the need of treatment was not confirmed at postnatal VI evaluation.

Interestingly, prenatal VI would have indicate treatment in 2 of 4 cases.

Fortunately, in all cases, physiological delivery was expected, which allowed all to reach full term gestational age and better adapt to extra uterine life.

However, using a measurement that is not fully reliable to decide the timing of delivery may not be the most correct choice in these cases.

Our proposal to resolve this problem is to use a different parameter during fetal ultrasound assessments, the prenatal VI. As reported before, VI is a reliable parameter usually utilized in postnatal cranial ultrasound assessment. Both VI and LVAD can be measured with ultrasound or magnetic resonance, therefore we conducted our comparison using MRI images.

In 11 of the 12 treated cases, the prenatal VI agreed with the postnatal VI indicating the need for treatment.

In not treated patients, prenatal and postnatal VI were concordant in 8 of 10 patients (7 of 9, considering the one not treated with VI of p97° + 10 mm). Accordance in not treatment patients between LVAD and postnatal VI was lower: 6 of 10 (5 of 9, considering the one not treated with VI of p97° + 10 mm).

Prenatal VI had an higher PPV than LVAD in recognize ventricular dilatation worthy of neurosurgical treatment (78.57% vs 70.59%).

As elicited by our data, NPV of LVAD and postnatal VI are higher than prenatal VI, reaching a percentage of 100%: if a ventriculomegaly is not found during pregnancy ultrasound scan, the future little patient certainly would not need to undergo neurosurgical treatment.

The current problem, however, concerns the correct decision about necessity of treatment for patients with ultrasound or MRI evidence of ventriculomegaly during uterine life.

It’s crucial to define a parameter to determine the requirement of a neurosurgical treatment in fetuses at an early gestational age, in order to plan the better timing of delivery to guarantee the best intrauterine development.

Introduction of prenatal VI could support, if not replace, LVAD.

This is the first attempt to standardize fetal and postnatal cerebral ventricles measures. The importance of finding a reliable parameter to define the need for neurosurgical treatment already during fetal life would certainly be of considerable use in defining the best timing of delivery. Surely the small sample we analyzed does not allow us to draw definitive

conclusions on the best method of measuring ventriculomegaly, but these interesting data allow us to start considering a different point of view to approach the disease.

LIMITATIONS

Our study has certainly several limitations.

First, his retrospective design did not allow us to collect complete information about maternal background (i.e. risk factors, placental pathology, number of ultrasound performed during the pregnancy) and about neurodevelopmental or neurosurgical outcomes of the babies. Also the wider geographical patients distribution, wasn't helpful to pursue an adequate follow-up.

Furthermore, no investigations have been carried out on coagulation alterations in mothers and newborns, especially as regards the search for genetic alterations.
These data would have been useful to shed light on the etiopathology of antenatal GMH-IVH where genetic predisposition to develop GMH-IVH may rely more often than postnatally on thrombophilia.

Another important limitation is related to the extremely low incidence of the disease: as it happens with other rare disease, is very difficult to have a cohort wide enough to be a statistical significant cohort.

CONCLUSION

In conclusion, our data suggest that fetal PVHD invariably result in permanent VPS placement compared to those who develop PHVD postnatally. Apart from the obvious delay in diagnosis fetal PHVD another possible explanation is the lack of common methods to measure and compare levels of dilatation of lateral ventricles. In addition the delay may depend also on the cautiousness in suggesting, by anticipating it, timing of delivery.

The greatest difficulty in fetal GMH-IVH and PHVD management is certainly represented by the scarce diagnostic and predictive tools for a neurosurgical treatment need.

Adopting a common measurement tool for obstetricians and neonatologists is of paramount importance for choosing the best moment of delivery, balancing the dangerous effects of preterm birth with the need for positioning a possibly temporary device to treat ventricular dilatation.

Future studies could shed some light on this pathology, to gain more knowledge also about IVH of preterm at postnatal onset.

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