Role of foetal MRI in the diagnosis and prognosis of cerebral ventriculomegaly assessed by prenatal ultrasonography

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Abstract

Introduction: Magnetic resonance imaging has been used as a valuable complement to prenatal ultrasonography in foetuses diagnosed with cerebral ventriculomegaly and, nowadays, this finding constitutes the major indication for foetal magnetic brain imaging. The role of this technique to further describe the disease, diagnose other associated abnormalities and predict future outcomes is a key point of study.

Objective: To evaluate the additional diagnostic and prognostic value of in-utero magnetic resonance imaging with regard to patients with a previous ultrasonographic diagnosis of foetal cerebral ventriculomegaly.

Materials and Methods: Cerebral magnetic resonance images and reports of 34 foetuses with a prenatal ultrasonography finding of cerebral ventriculomegaly were evaluated and reports of both examinations were compared. When possible, prenatal magnetic resonance results were compared to postnatal diagnoses obtained by clinical examination (gestational age at birth, Apgar score, head circumference and Ruth-Griffiths developmental assessment) and imaging studies (transfontanelar US and cerebral magnetic resonance imaging). In cases of interrupted pregnancies, prenatal reports were compared to the autopsy reports.

Results: Foetal magnetic resonance images confirmed 85.7% of the ultrasonography diagnoses and in 32.4% of these cases, both prenatal imaging techniques were in complete agreement. Magnetic resonance imaging increased the diagnosis of associated ventriculomegalies from 4 to 15 cases, and provided additional information in 13 foetuses. There was a positive correlation between associated and severe ventriculomegalies. In 8 out of 17 cases, foetal magnetic resonance diagnosis was
confirmed by postnatal transfontanelar ultrasonography and 7 of these confirmed by postnatal cerebral magnetic resonance. From the cases followed after birth, more than half were considered normal (without ventriculomegaly), most of them associated to prenatal diagnoses of mild/moderate and isolated ventriculomegalies. Five out of 7 infants obtained a below average result on the neurodevelopment test, most of them with a prenatal diagnosis of severe and associated ventriculomegaly. All autopsy reports coincided with the foetal MRI diagnoses and terminated pregnancies were directly related to cases of associated and severe ventriculomegalies.

**Conclusion:**

Foetal magnetic resonance imaging is an important adjunct to prenatal US and its key role lies in the diagnosis of associated lesions, that are frequently not detected by ultrasonography and represent cases with worse prognosis.

**Key-Words:** prenatal diagnosis; cerebral ventriculomegaly; ultrasound imaging; magnetic resonance imaging; pregnancy outcome; perinatal outcome; developmental outcome

**Word count:** 3019
Introduction

Ultrasound imaging (US) is the standard screening modality for initial evaluation of the foetal central nervous system and its anomalies such as ventricular enlargement\(^1\). It is safe for both foetus and mother, relatively inexpensive, allows real-time imaging and is readily available\(^2\). Nonetheless, it is important to acknowledge that its diagnostic value may be diminished by technical factors limiting visualisation of the side of the brain near the transducer or the posterior fossa, complex foetal anomalies or poor visualisation of the foetus due to large maternal habitus or oligohydramnios\(^1,2\).

Magnetic resonance imaging (MRI) is a valuable complement to US in foetuses with difficult US-based diagnoses or when additional information is needed for the decision-making processes during pregnancy. The potential of foetal MRI was first described in 1983 by Smith et al\(^3\). Early attempts were disenchanted by the long examination times and the need to sedate both mother and child to reduce foetal movement that could interfere with the quality of the exam\(^4\). Over the past decade, technological developments have allowed ultra fast imaging sequences with significant fewer motion problems avoiding the need for sedation or anaesthesia\(^5\). Nowadays, foetal cerebral ventriculomegaly (VM) constitutes the major indication of foetal brain MRI\(^6\).

VM indicates the presence of an excess of fluid in the lateral ventricles of the developing brain\(^6\). It is diagnosed when the width of one or both ventricles, measured at the level of the atria, is \(\geq 10 \text{mm}\)\(^6\). Gaglioti et al. (2005) divide this abnormality in: 1) mild VM (10-12mm); 2) moderate VM (12.1-14.9mm); and 3) severe VM
It can be further divided into unilateral or bilateral VM and isolated or associated VM\textsuperscript{1}. Three general processes may result in the formation of VM including abnormal turnover of the cerebrospinal fluid (CSF), abnormality of cerebral development and destructive processes\textsuperscript{6}.

It has been described to be associated with other foetal anomalies, both neuronal and somatic, in 70-85\% of cases\textsuperscript{7} being the rate of associated malformations higher (\geq 60\%) in severe VM and lower (10-50\%) in cases of mild and moderate VM\textsuperscript{6}. This ventricular enlargement is also related to an increase in foetal and neonatal morbidity and mortality, however, this is probably due to the related abnormalities rather than the VM itself, implying that associated lesions carry a worse prognosis\textsuperscript{1}. Additionally, studies report that unilateral VM have lower perinatal morbidity and mortality, as well as lower association with other CNS or non-CNS anomalies when compared to bilateral VM\textsuperscript{1}.

There is a good neurodevelopmental outcome in most (90\%) newborns with prenatal diagnosis of isolated VM with diameter between 10-12mm, being less favourable when >12mm\textsuperscript{6}. Furthermore, studies have shown that there is a higher likelihood of developmental delay in subjects with associated anomalies (56\%) compared to those with isolated mild VM on US\textsuperscript{1}.

It is therefore of utmost importance to investigate a foetal cerebral VM and its associated lesions, in order to provide a correct guidance during pregnancy and predict prognosis for the future newborn\textsuperscript{8}. Although the diagnosis is usually easily and accurately made using US, the consequences are more complicated, as associated
anomalies may be missed even by experienced hands, making accurate counselling difficult$^4$. The capacity of foetal MRI to further characterise the VM and diagnose other associated abnormalities is an aim to determine the role of this imaging exam as an adjunct to US.
Methods

Subjects:
The patients in this study were selected if they had attended the MRI unit of the Neuroradiology department at Centro Hospitalar do Porto-Hospital de Santo António (CHP-HSA) for in-utero imaging, between 2006 and 2011, after an US diagnosis of foetal cerebral VM, made by a foetal US specialised obstetrician at CHP-Maternidade Júlio Dinis (CHP-MJD). Thirty-four patients were included.

Procedure:
A retrospective analysis was carried out of foetal MRI reports and their corresponding prenatal US reports with the diagnosis of VM, obtained by searching the electronic patient database (SAM) and patient file archive of CHP-HSA and CHP-MJD. For each patient, the gestational age at the time of the first diagnostic US was recorded. All foetal MRI exams were performed using a GE Signa 1.5T MRI system. On the images obtained by MRI the lateral ventricles were measured at both an axial and coronal section at the level of the ventricular atria. On both US and foetal MRI reports the VM was classified as: mild (10-12mm), moderate (12.1-14.9mm) or severe (>15mm); isolated or associated to another lesion; bilateral or unilateral. The overall information on the US reports was compared to that on the MRI reports and annotated if US and MRI diagnosis coincided, did not coincide and when MRI brought additional information. When available, the postnatal diagnosis was compared to the prenatal MRI result. In live-born infants, this diagnosis was obtained by clinical examination including gestational age at birth (considered normal if ≥37 weeks), Apgar test (low risk if ≥7 and ≥9 at the 1st and 5th minutes respectively) and head circumference at birth and 12 months (normal if between the 3rd and 97th percentile)
and imaging studies (transfontanelar US and cerebral MRI). In cases of interrupted pregnancies the autopsy reports were obtained.

Furthermore, when the infants were followed at the paediatric department of CHP-HSA, the results of the Ruth-Griffiths developmental assessment were also obtained.

**Statistical analysis:**

The software package used for all statistical analysis was *SPSS version 19.0.0.*

Descriptive analysis (including mean, standard deviation, frequencies, crosstabs and graphical presentations of results) was obtained and normality tests, such as Shapiro-Wilk test, were calculated. For group comparisons, Spearman’s rank correlation coefficient, Mann-Whitney-U test and Kruskal-Wallis test were employed according to the samples’ characteristics (independent, non-normal distributed variables).

**Ethical issues:**

This study was submitted to and approved by the Ethical Health Committee of CHP.
Results

The majority of the foetuses with VM were male (figure 1) and the mean gestational age at prenatal US diagnosis was 27 weeks. The Shapiro-Wilk test was applied to the quantitative variables showing that they are all non-normal distributed variables (table I).

Prenatal diagnosis

According to all 34 prenatal US reports collected, 12 VM were classified as moderate to severe and 22 as mild, 21 bilateral and 13 unilateral, 4 as associated to another lesion and 30 isolated.

In comparison, of the 34 VM cases diagnosed by US, MRI confirmed 29 cases (85.3%) and considered the other 5 cases as normal (lateral ventricles with normal size and shape). Similar to what was shown by prenatal US, 11 cases were classified as moderate to severe and 18 as bilateral. On the other hand, 15 cases were associated to another pathology, increasing the percentage of associated cases from 11.8% in prenatal US to 50% in foetal MRI, 53.3% of them (8 cases) being associated to agenesis of the corpus callosum (ACC). The majority of VM continued to be classified as mild by foetal MRI (52.9%).

A significant positive correlation between prenatal US and foetal MRI severity grade was found ($R^2_{33}=0.355$, $p=0.043$). Figure 2 and 3 demonstrate the classification of VM diagnosed by prenatal US and foetal MRI respectively.
Foetal MRI brought additional information to prenatal US diagnosis in 13 foetuses (38.2%), 7 had additional diagnosis of ACC (Figure 4). Table II summarises these cases.

This imaging modality also showed a statistically significant positive relation between associated and severe VM ($R_{29}=0.405$, $p=0.029$). Moreover, associated VM cases were directly related to bilateral VM with a 90% confidence level ($p=0.082$). In respect to distribution by gender, figures 5-8 show that only 1 female foetus had a VM classified as severe by MRI in comparison to 5 males, yet, in proportion, a higher percentage of females had severe and/or bilateral cases.

**Autopsy findings**

Four pregnancies were terminated due to foetal abnormalities and according to autopsy reports, in every case the foetal MRI diagnosis was confirmed, as can be seen in table III. Three out of 4 of these cases were diagnosed as isolated by prenatal US.

**Postnatal diagnosis**

Of the 34 foetuses initially followed, and excluding the 4 cases of interrupted pregnancies, 23 babies are known to have been live births and in 7 cases follow-up of the pregnancy was lost.

Delivery was at a mean gestational age of 37 weeks and 86.7% were considered full-term pregnancies (37 weeks or above according to *Sociedade Portuguesa Neonatologia*). Preterm births were related to foetuses with a US prenatal diagnosis of
associated VM (p=0.011) and new-borns with diagnosis of severe VM on postnatal exams (p=0.070).

All live new-borns had an Apgar test with low-risk results and head circumference (HC) measurements were found altered in 4 cases at birth and 3 cases at 12 months, mostly related to cases of mild VM.

Seventeen babies were subsequently followed by postnatal transfontanelar US at a mean age of 8 weeks. Only 8 cases had VM confirmed, 62.5% severe, 100% bilateral and 75% associated (figure 9). Six out of 9 cases of VM not confirmed by transfontanelar US were classified as mild and isolated in prenatal exams.

Cerebral postnatal MRI confirmed the diagnosis of VM in 7 of the 8 cases confirmed by transfontanelar US (figure 10) providing additional information to prenatal diagnosis in 4 cases. The mean age at the time of the exam was 13 months. Most confirmed and not confirmed cases corresponded, with a 90% confidence level (p=0.083), to VM prenatally diagnosed as associated to another lesion and isolated VM, respectively.

More than half of foetal VM were not confirmed by postnatal exams. Cases diagnosed as “normal” on postnatal exams were related to cases classified as mild or moderate (p=0.006) and isolated (p=0.060), whilst confirmed cases were more often severe (p=0.006) and associated VM (p=0.060), with a 90% confidence interval.
Paediatric psychologists at CHP followed 7 of the 8 infants with the transfontanelar US diagnosis of VM (6 males and 1 female). By the time of the exam, the infants had a mean age of 25 months. The Ruth-Griffiths developmental assessment showed results below average in 71%, all of them being male infants (figure 11). Tables IV e V summarise the foetal MRI diagnosis of the children that underwent the neurodevelopment test, showing that most cases with below average results had severe VM and/or VM associated to another lesion.
Discussion

Prenatal diagnosis

From the sample description it is possible to conclude that more male foetuses were diagnosed with VM, although it was only possible to obtain information about foetus gender in 26 out of the 34 cases. Mild VM predominated in both US and MRI reports. Gaglioti et al. (2005) had already described a prevalence of male foetuses with VM.

Foetal MRI confirmed most of the VM diagnoses made by prenatal US. Nevertheless, in 5 cases it excluded this pathology, showing that MRI may be useful to confirm but as well to exclude VM, avoiding the anxiety and further controls generated by a this diagnosis\(^6\). However, it is important to refer that false positive prenatal US diagnoses could be due to the regression of the VM during foetal life in some cases (Gaglioti et al. 2005). VM seems to be among the most common false positive diagnoses at US screening for foetal malformations\(^6\).

As already stated, US and MRI VM diagnoses showed a good correlation. However, only 11 cases (32.4%) had the exact same diagnosis on both prenatal exams (matching severity, uni/bilaterality and association), all being mild or moderate. The fact that eleven cases (36.6% of all isolated VM) had their US isolated VM diagnosis altered to associated VM suggest that MRI could provide a more accurate detection of associated malformations. Other studies have already showed that MRI is superior to ultrasound in detecting parenchymal damage, migrational abnormalities, infarction, germinal matrix hemorrhage and intraventricular hemorrhage, but not other lesions for which a dedicated neurosonographic examination could be superior, such as choroid plexus cysts\(^9\).
Overall foetal MRI brought additional information to prenatal US in a reasonable percentage of cases (38%) showing that it seems to be an important adjunct to US. In 7 out of 13 cases the additional findings included ACC remarking the importance of this imaging modality in this disease’s diagnosis. Other studies have already shown that half of associated malformations correspond to ACC\textsuperscript{11}.

As already discussed in this study, cases of VM associated to another pathology, usually carry a worse prognosis and are more often bilateral and severe\textsuperscript{1}. This was confirmed by the foetal MRI results that showed a statistically significant positive correlation between associated VM and severe and bilateral VM.

**Autopsy Findings**

Foetal MRI proved to be accurate in the prognosis of the disease as all of the diagnoses were confirmed by the autopsy reports. It was concluded that foetal MRI was useful for the decision making process as in 3 out of 4 cases, prenatal US had diagnosed the VM as being isolated and MRI altered the diagnosis to associated to a severe malformation.

The presence of an associated pathology can determine pregnancy interruption\textsuperscript{1}; therefore, if foetal MRI brings additional information about these associated malformations, it has an important role in the pregnancy’s outcome.
Postnatal Findings

According to statistical tests, it was clear that association to another cerebral malformation and bilaterality carry a worse prognosis and end more frequently in abortion, as was also described by Gaglioti et al (2005). It is known, and reinforced by this study’s results, that a statistically significant number of VM associated to other lesions are also bilateral and severe, therefore, the worse prognosis of these VM might be associated to the morbidity and mortality directly related to the associated lesion, rather than to the VM itself\(^1\). It is also important to highlight that in 7 cases the pregnancies’ outcomes were unknown due to follow-up loss, lowering the sample’s size.

VM prenatally diagnosed as associated were linked to preterm births and to the diagnosis of severe VM on postnatal exams, contributing to the conclusion that associated VM are more severe and have worse pregnancy outcomes\(^1\).

No significant correlation was found between foetal MRI findings and the Apgar results although it seems important to stress that no newborn had the need for reanimation manoeuvres at birth. Concerning the HC at birth and 12 months, 3 out of 4 cases with macrocephaly had the prenatal diagnosis of mild VM. This is contrary to what was expected as literature shows that moderate/severe and associated VM are more often related to newborns with macrocephaly and hydrocephalus\(^5\).

Postnatal transfontanelar US and cerebral MRI proved to be useful in correcting VM diagnosis in newborns. With transfontanelar US, only 8 cases were diagnostic and, of these, 7 confirmed by postnatal cerebral MRI. This means that foetal MRI, although
altering some prenatal US VM diagnoses, may still overestimate the value of VM. Most of the cases not confirmed by postnatal exams corresponded to mild and isolated VM. It is important to recall the study of Gaglioti et al. (2005) that stated that the lower number of VM diagnosed by both foetal MRI and postnatal studies might be due to the regression of VM during foetal life. Different criteria apply to the analysis of VM in foetuses and newborns, and mild/isolated foetal VM might not be important to value in an infant, whereas all VM must be described in uterus to discard other abnormalities.

A case control study (Bloom et al. 1997) compares the outcome of foetuses with borderline VM and foetuses with normal ventricular width, showing a significant lower mental and psychomotor development in the former group. A severe and associated VM diagnosed prenatally by foetal MRI predicted a worse result in the Ruth-Griffiths developmental assessment, carried-out at a mean age of two years old. In spite of that, it is important to point out that in this study, only children with a postnatal VM diagnosis were submitted to neuropsychological tests. Even so, this test is standardised and results can be compared to values of a normal control population.

Pilu et al. (1999) reported better neurodevelopmental outcomes in male compared with female foetuses with VM, although, overall, this anomaly affects more males than females. This finding would suggest that male foetuses have slightly larger ventricular width compared to females. In comparison, all bellow average neurodevelopmental results in this study belonged to male children, even though no significant conclusion could be taken due to the small female sample.
Limitations

Every study with a small sample leads to a greater difficulty obtaining statistically significant results and may be further impaired by the existence of “missing values” in many variables. These were the major limitations of this study. Also, some tests (such as postnatal MRI) were only carried out if there was already a preexisting malformation diagnosed by previous exams, creating a bias.

Follow-up of the pregnancy was lost in many cases and, moreover, many newborns were not followed by paediatrics at CHP leading to a great number of case losses.

Furthermore, US and MRI reports were not all carried out by the same physician. Although protocols are made for the measurement of the lateral ventricles, this may still generate a variability and subjectivity in the interpretation.

This study has, therefore, all the disadvantages inherent to a retrospective study and, for future recommendations, a prospective study should be carried out to further estimate the role of foetal MRI in VM previously assessed by US.
**Conclusion**

Foetal MRI is an important adjunct to prenatal US providing both confirmation and additional information in the majority of cases of VM, being also useful in the exclusion of false positive results. It is clear that foetal cerebral MRI carries great value in the diagnosis of associated lesions that are not detected by US. The cases with associated anomalies (that tend to be associated to more severe and bilateral VM) had worse prognosis: pregnancy interruption, VM confirmed by postnatal exams, and poorer neurodevelopmental results.

As foetal MRI brings more information to the diagnosis of these associated cases, helps to make decisions concerning the pregnancy and predict outcomes, it shows an important role in this disease’s study.
We acknowledge João Xavier PhD, director of the Neuroradiology service at CHP for the expertise and providing the means needed for the study’s elaboration. We also acknowledge Sofia Pina MSc (neuroradiologist) and Luísa Ferreira MSc (obstetric ultrasonographer) for the support. We thank Vera Araújo for assistance with statistical analysis.
References

### Table legends:

#### Table I- Normality tests

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<th>Shapiro-Wilk</th>
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<td>Statistic df Sig.</td>
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<td>Prenatal US severity</td>
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<td>Prenatal US laterality</td>
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<td>0.617 34 0.000</td>
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<td>Prenatal US association</td>
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<sup>a</sup> Lilliefors Significance Correction

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<td>Foetal MRI laterality</td>
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<sup>a</sup> Lilliefors Significance Correction

### Tests of Normality<sup>b</sup>

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<td>0.724 8 0.004</td>
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<td>Transfontanelar US association</td>
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<td>0.566 8 0.000</td>
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<sup>a</sup> Lilliefors Significance Correction

<sup>b</sup> Transfontanelar US uni/bilaterality is constant. It has been omitted.

### Tests of Normality

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<td>Gestation at VM diagnosis (weeks)</td>
<td>0.221 12 0.109</td>
<td>0.919 12 0.278</td>
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<td>Gestation at birth (weeks)</td>
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<td>Age at exam (weeks)</td>
<td>0.189 12 0.200</td>
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<sup>a</sup> Lilliefors Significance Correction

* This is a lower bound of the true significance.
Table II- Foetal MRI additional diagnoses

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<tr>
<th>Foetal MRI diagnosis</th>
<th>Cases</th>
<th>Percent</th>
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<tr>
<td>Agenesis of corpus callosum</td>
<td>7</td>
<td>41%</td>
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<tr>
<td>Intrahemispheric cyst</td>
<td>2</td>
<td>12%</td>
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<tr>
<td>Hypoplasia of the corpus callosum</td>
<td>1</td>
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<tr>
<td>Absence of septum pellucidum</td>
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<td>6%</td>
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<tr>
<td>Arnold-chiari malformation</td>
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<td>6%</td>
</tr>
<tr>
<td>Dandy-Walker malformation</td>
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<td>6%</td>
</tr>
<tr>
<td>Cortical development anomaly/ bilateral frontal displasia</td>
<td>1</td>
<td>6%</td>
</tr>
<tr>
<td>Mega cisterna-magna</td>
<td>1</td>
<td>6%</td>
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<tr>
<td>Cortical and periventricular destructive lesion</td>
<td>1</td>
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<tr>
<td>Romboencefalosinapsis</td>
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<td>6%</td>
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Table III- Autopsy findings

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<tr>
<td>Dandy- Walker malformation</td>
<td>Dandy-Walker malformation confirmed</td>
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<td>Complete agenesis of the corpus callosum. Typical colpocephalic enlargement of the lateral ventricules</td>
<td>Confirmed agenesis of the corpus callosum and severe bilateral ventriculomegaly</td>
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<tr>
<td>Complete agenesis of the corpus callosum. Typical colpocephalic enlargement of the lateral ventricules associated to the absence of the septum pellucidum</td>
<td>Confirmed agenesis of the corpus callosum and severe bilateral ventriculomegaly</td>
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<td>Mild isolated bilateral VM associated to romboencefalosinapsis</td>
<td>Confirmation of romboencefalosinapsis</td>
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Table IV - Foetal MRI findings vs Ruth Griffiths Development Assessment results

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<tr>
<th>Foetal MRI findings</th>
<th>Ruth Griffiths Test result</th>
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<tr>
<td></td>
<td>Average</td>
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<tr>
<td>Severity</td>
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<td>Mild</td>
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<td>Association</td>
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Table V - Foetal MRI findings vs Ruth Griffiths Development Assessment Results

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<tr>
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<td>Average</td>
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<tr>
<td>Moderate bilateral isolated VM</td>
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Table VI- Correlation between imaging modalities (prenatal US, foetal MRI, transfontanelar US)

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<th>Prenatal US findings</th>
<th>Foetal MRI findings</th>
<th>Transfontanelar US findings</th>
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<tr>
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*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).
Figure Legends

Figure 1- VM distribution by gender

*- In this study, it was only possible to collect gender in 26 out of the 34 cases.

Figure 2- Prenatal US findings
Figure 3- Foetal MRI Findings

- Normal
- Mild unilateral associated VM
- Mild bilateral associated VM
- Moderate bilateral associated VM
- Severe bilateral isolated VM
- Mild unilateral isolated VM
- Mild bilateral isolated VM
- Moderate bilateral isolated VM
- Severe unilateral associated VM
- Severe bilateral associated VM

Figure 4- Extra-information provided by foetal MRI

- No: 38.2%
- Yes: 61.8%
Figure 5- Foetal MRI findings by gender

*In this study, it was only possible to collect gender in 26 out of the 34 cases.

Figure 6- Severity by gender in foetal MRI findings

* In this study, it was only possible to collect gender in 26 out of the 34 cases. In this figure only 21 VM are shown, as 5 out of the 26 were considered normal.
*In this study, it was only possible to collect gender in 26 out of the 34 cases. In this figure only 21 VM are shown, as 5 out of the 26 were considered normal.

*In this study, it was only possible to collect gender in 26 out of the 34 cases. In this figure only 21 VM are shown, as 5 out of the 26 were considered normal.
Figure 9- Transfontanelar US findings

Figure 10- Postnatal MRI findings vs postnatal transfontanelar US findings

- Ventricular enlargement confirmed
- Ventricular enlargement not confirmed
Figure 11 - Ruth Griffiths Developmental Assessment results

- Average: 71.4%
- Below average: 28.6%

Figure 12 - Prenatal US and Foetal MRI findings

- Mild: 18
- Moderate: 5
- Severe: 6
- Unilateral: 11
- Bilateral: 18
- Isolated: 14
- Associated: 15
- Diagnostic: 5

- Severity
- Laterality
- Association
- Normal

- Prenatal US
- Foetal MRI
Figure 13- Transfontanelar ultrasonography: coronal plane showing slightly enlarged anterior horns of the lateral ventricles (arrow).
Figure 14- Foetal MRI showing mild ventriculomegaly associated to corpus calosum agenesis
Figure 15- Foetal MRI showing moderate bilateral ventriculomegaly
Appendix 1

Resumo Circunstanciado em Língua Portuguesa

Titulo

Valor diagnóstico e prognóstico da ressonância magnética fetal na investigação de ventriculomegalias cerebrais diagnosticadas por ecografia pré-natal.

Introdução

A ressonância magnética (RM) é um valioso complemento à ecografia pré-natal quando é necessária informação adicional para o correto diagnóstico e tomadas de decisões durante a gravidez¹. A ventriculomegalia cerebral (VM) corresponde a um ventrículo lateral em desenvolvimento com uma largura, ao nível do átrio, igual ou superior a 10mm², representando a indicação mais frequente para a realização de RM cerebral fetal³. Esta alteração pode ser classificada em ligeira, moderada ou grave, unilateral ou bilateral, isolada ou associada a malformações do sistema nervoso central. Os casos de VM moderada e severa estão mais vezes associados a outras patologias e, logo, com prognóstico mais sombrio a curto e longo prazo (Gaglioti et al. 2005).

O objetivo deste estudo é avaliar o valor diagnóstico e prognóstico da RM fetal em casos de VM previamente diagnosticada por ecografia pré-natal.
Método e Amostra

Amostra

Foram selecionadas as grávidas com diagnóstico de VM cerebral fetal, efetuado por ecografia (realizado por médico obstetra no Centro Hospitalar do Porto CHP-Maternidade Júlio Dinis), e que tivessem sido submetidas a RM fetal no Departamento de Neuroradiologia do CHP entre os anos 2006 e 2011.

Trinta e quatro grávidas corresponderam a estes critérios

Metodologia

Avaliação dos relatórios e imagens das RM e ecografias cerebrais fetais efetuadas às grávidas selecionadas, através da análise dos processos clínicos (eletrónico e em papel) e de aplicações informáticas transversais (SAM, SECTRA). Comparadas as dimensões dos ventrículos cerebrais laterais registadas pela ecografia e RM cerebral, bem como as características descritas: as VM foram classificadas como ligeiras (10-12mm), moderadas (12.1-14.9mm) ou severas (>15mm); unilaterais ou bilaterais; isoladas ou associadas a outras malformações do sistema nervoso central (SNC) em cada relatório.

A análise dos resultados pré-natais foi complementada, sempre que possível, com análise de resultados imagiológicos pós-natais (RM cerebral e ecografia transfontanelar) ou relatórios de anatomia patológica em caso de interrupção da gravidez (IG).

A caracterização pós-natal avaliou os seguintes parâmetros: idade gestacional ao nascimento (considerada normal se ≥37 semanas), resultado teste Apgar (sem risco
acrescido se ≥7 e ≥9 ao 1º e 5º minutos respectivamente) e valores de perímetro cefálico ao nascimento (normais se entre percentil 3 e percentil 97). Estas classificações seguem as preconizadas pela Sociedade Portuguesa de Neonatologia. Outros dados clínicos pesquisados para avaliar as repercussões clínicas, comparando com o diagnóstico pré-natal, incluíram a avaliação do perímetro cefálico aos 12 meses, e os resultados do Teste de Desenvolvimento Mental de *Ruth-Griffiths* nos casos em que as crianças mantiveram seguimento no serviço de Pediatria do CHP - análise também obtida através da consulta dos processos clínicos (eletrónico e em papel) e de aplicações informáticas transversais (SAM, SECTRA).

**Análise de Dados**

Na análise estatística foi utilizado o programa SPSS versão 19.0.0. A análise de dados foi iniciada pela estatística descritiva, incluindo médias, desvio de padrão, frequências, apresentação gráfica de resultados e crosstabs. Testes de normalidade, nomeadamente o teste de Shapiro-Wilk, foram aplicados às variáveis quantitativas e, para fins de comparação de grupos, o coeficiente de Spearman e os testes de Mann-Whitney-U e Kruskal-Wallis foram usados de acordo com as características da amostra (variáveis independentes sem distribuição normal).

**Princípios Éticos**

Este trabalho foi submetido para avaliação pela Comissão de Ética para a Saúde do CHP, tendo sido aprovado pela mesma entidade.
**Resultados**

Foi notória uma prevalência de fetos do sexo masculino com o diagnóstico de VM, apesar de maior percentagem de fetos do sexo feminino ter VM mais severa e bilateral. O teste de Shapiro-Wilk mostrou tratar-se de uma amostra com variáveis sem distribuição normal.

**Diagnóstico Pré-natal**

Dos 34 relatórios ecográficos obtidos as VM foram distribuídas pelas seguintes classificações: 12 com gravidade moderada a severa e 22 ligeiras, 21 bilaterais e 13 unilaterais, 30 isoladas e 4 associadas a outras malformações (ausência de corpo caloso, ausência do *septum pellucidum*, cerebelo em forma de “banana” e hipoplasia do cerebelo).

Em 34 relatórios de ressonância magnética fetal, o diagnóstico ecográfico de VM foi confirmado em 29 casos (85,3%) e excluído em 5. A maior diferença na classificação das VM em ambas as técnicas de imagem ocorreu no grupo das VM associadas a outra patologia. A RM fetal classificou 15 casos como associados a outras lesões aumentando a percentagem destes casos de 11,8% na ecografia para 50% na RM, 8 destes associados a agenesia do corpo caloso.

Foi estatisticamente provado que quanto maior a severidade da VM na ecografia pré-natal, maior a severidade da doença na RM fetal (RS$_{33}$=0,355, p=0,043). Da mesma forma, foram reveladas relações estatisticamente significativas entre VM associadas e VM severas e bilaterais (RS$_{29}$=0,405, p=0,029; p=0,082).
Dados de Autópsia

Em 4 casos houve interrupção induzida da gravidez, sendo que, em todos estes os relatórios das autópsias e da RM fetal foram coincidentes a nível de diagnóstico. Os casos de IG consistiram maioritariamente de VM severas e associadas a outras malformações. Em 3 destas situações, a RM fetal tinha alterado o diagnóstico da ecografia pré-natal de VM isolada para associada.

Diagnóstico Pós-natal

Para além das 4 IG, há relato de 23 recém-nascidos e 7 casos com perda de follow-up.

Da totalidade dos nascimentos de que se obteve registo, 86,7% corresponderam a partos de termo (≥37 semanas, segundo a Sociedade Portuguesa de Neonatologia) e, os restantes, a partos pré-termo relacionados estatisticamente com casos classificados como associados a outra patologia na ecografia pré-natal (p=0,011) e, posteriormente como VM severas nos exames pós-natais (p=0,070).

O teste de Apgar mostrou-se sem risco acrescido em todos os recém-nascidos e os casos com perímetro cefálico alterado ao nascimento ou aos 12 meses corresponderam principalmente a VM classificadas como ligeiras.

Dos 17 casos seguidos por imagiologia pós-natal, 8 obtiveram diagnóstico de VM na ecografia transfontanelar e destes, 7 confirmados por RM cerebral. Seis dos 9 casos não diagnosticados por exame transfontanelar correspondiam a VM ligeiras e isoladas em diagnósticos pré-natais. RM cerebrais pós-natais ofereceram informação adicional em 4 casos. Diagnósticos pré-natais de VM confirmados por RM foram relacionados a casos associados a outras lesões (p=0.060), e a casos severos (p=0.006) com um intervalo de confiança de 90%.
Sete das oito crianças com dilatação ventricular confirmada por exames pós-natais foram seguidas na consulta de pedopsicologia do CHP. Cinco (71%) obtiveram resultados abaixo da média no *Ruth-Griffiths developmental assessment*, correspondendo todos a casos do sexo masculino, tendo a maioria um diagnóstico, feito por RM pré-natal, de VM severa e/ou associada.
Discussão

Diagnóstico Pré-natal

Apesar da limitação do tamanho da amostra, este estudo aponta para uma prevalência de VM no sexo masculino, já como tinha sido descrito por Gaglioti et al. (2005). Estes autores tinham também denotado um aumento de casos de partos pré-termo em fetos com o diagnóstico de VM, principalmente se severa e associada a outras patologias. Este facto não foi corroborado pelo presente estudo visto que a média de tempo de gestação ao nascimento foi de 37 semanas (considerada normal de acordo com a Sociedade Portuguesa Neonatologia).

Foi também indicado que a maioria das VM tendem a ter uma severidade ligeira.

A RM fetal revelou-se importante para a exclusão de alguns casos falsamente diagnosticados por ecografia, podendo evitar uma situação potencialmente geradora de ansiedade durante a gravidez. No entanto, importa referir que existe a possibilidade de regressão espontânea da VM durante a gravidez, principalmente se ligeiras e isoladas.

Apesar de ser notória uma boa correlação geral entre diagnóstico pré-natal ecográfico e por RM fetal, o facto de apenas 11 casos (32,4%) serem totalmente compatíveis (na classificação de severidade, uni/bilateralidade e associação a outras patologias) e o incremento tão pronunciado de casos associados, sugerem que a RM é mais eficaz na deteção de casos com associação a outras alterações, trazendo informação adicional à ecografia em 38% dos casos. Em mais de metade, a patologia associada correspondeu a agenesia do corpo caloso, mostrando a importância desta modalidade de imagem no diagnóstico desta malformação.
Foi também sublinhado, através dos resultados da RM fetal, que, como seria esperado, casos associados a outra patologia têm VM mais severa e/ou bilateral acarretando um pior prognóstico.

**Dados de Autópsia**

A RM fetal mostrou eficácia no prognóstico de VM e suas doenças associadas, visto que todos os diagnósticos foram confirmados nos relatórios de autópsia e 3 diagnósticos de VM isoladas obtidos por ecografia foram alterados para VM associadas a outras patologias pela RM fetal, justificando a realização de IG.

**Diagnóstico Pós-natal**

Está bem patente neste estudo que associação a patologia e bilateralidade estão correlacionados a pior prognóstico, como já tinha sido descrito por Gaglioti et al (2005). Este facto poderá estar relacionado com a morbidade e mortalidade inerentes às patologias associadas e nem tanto à VM em si. O pior prognóstico destas VM foi também corroborado pela grande proporção destes diagnósticos nos partos que ocorreram pré-termo.

Quanto ao perímetro cefálico, dos raros casos com macrocefalia após o nascimento ou aos 12 meses, ao contrário do que seria esperado, a maioria correspondeu a casos de VM diagnosticadas no período pré-natal como ligeiras. Na literatura, VM moderadas/severas e associadas a outras patologias, são descritas como as mais frequentemente ligadas a macrocefalia e hidrocefalia.

A imagiologia pós-natal mostrou-se importante na confirmação e exclusão de casos diagnosticados no período pré-natal. O facto de apenas 8 casos terem sido confirmados por ecografia transfontanelar e, destes, 7 confirmados por RM cerebral,
mostrou que a RM fetal, apesar de útil na exclusão de alguns possíveis falsos-positivos na ecografia fetal, ainda sobrevaloriza esta alteração em alguns casos. Esta sobrevalorização pode ser propositada pois VM ligeiras e isoladas podem não ser de valorizar em recém-nascidos mas todas a VM devem ser descritas na RM fetal para haver certeza que esta não está associada a outra patologia com consequências mais graves. No entanto, os exames pós-natais mantêm-se importantes fontes de informação adicional.

Como já referido, a RM fetal provou ser mais valiosa no diagnóstico de VM associada a outras patologias, principalmente agenesia do corpo caloso, e estes foram os casos que mais frequentemente corresponderam às situações posteriormente confirmadas nos exames pós-natais. Os casos não confirmados relacionaram-se com casos mais leves e isolados de VM. Relembramos o estudo de Gaglioti et al (2005) e o facto de existir relatos de regressão espontânea da alteração no período fetal, sendo que são os casos isolados e unilaterais os mais associados a este desaparecimento.

Um diagnóstico pré-natal de VM severa ou associada feito por RM fetal previu um resultado mais precário no estudo de neurodesenvolvimento pós-natal, realizado às crianças com uma média de 2 anos de idade.

Pilu et al. (1999) descreveram resultados de neurodesenvolvimento mais favoráveis no sexo masculino em comparação com o feminino, apesar do maior número do casos de VM em meninos, sugerindo que estes apresentam, normalmente, dimensões ventriculares maiores que as meninas. Contrariamente, todos os resultados abaixo da média neste estudo pertenciam a crianças do sexo masculino, apesar de não se poder tirar nenhuma conclusão significativa devido à pequena amostra de casos do sexo feminino.
Limitações

A maior limitação deste estudo assenta no pequeno número da amostra e na existência de diversos casos não acompanhados no período pós-natal, gerando uma grande dificuldade na obtenção de resultados estatisticamente significativos. Da mesma forma, o facto de muitos exames apenas serem realizados mediante um diagnóstico prévio de alterações em exames anteriores é gerador de um importante viés.

Outro ponto fraco reside na heterogeneidade dos relatórios realizados por diferentes especialistas com diferentes técnicas de análise e descrição de lesões (apesar das tentativas de padronização das medições dos ventrículos cerebrais através de protocolos), gerando subjetividade na interpretação das imagens.

Este estudo apresenta, portanto, todas as desvantagens inerentes a uma análise retrospectiva e é sugerida a realização de um trabalho prospetivo para aprofundamento do tema

Conclusão

A RM fetal é um importante método de imagem adjuvante à ecografia fetal no diagnóstico de VM. O seu papel fulcral assenta no diagnóstico de malformações associadas a esta alteração, frequentemente mal-interpretadas pela ultrassonografia, que acarretam um pior prognóstico e predizem maiores sequelas na futura criança.
Referências Bibliográficas


