A systematic review of prenatal diagnosis Vein of Galen aneurysm: prenatal predictive markers and management from the fetal life to childhood

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Abstract

Background

Vein of Galen malformations (VGMs) account for less than 1% of all intracranial vascular malformations. However in the fetal and pediatric population represent the most common vascular malformation of the brain. An optimal knowledge of the prenatal and postnatal clinical features is mandatory for an effective management.

Methods

Articles published between 1st January 2003 and 1st January 2023, reported in PUBMED and EMBASE, were evaluated for a systematic review analyzing prenatal features, postnatal features and management of fetal Galean VGMs.

Results

Twenty-nine papers reporting information on 50 prenatally-diagnosed VGM were included. The most common prenatal features were: fetal hydrocephalus (40%) and cardiomegaly (58%). Post-natal data of 42 VGMs cases are described. The overall mortality was 59.52%. 76.50% of the survivors had a normal development.

Conclusions

A close follow-up and a multidisciplinary approach is mandatory to manage this condition. The aim of our study was to provide a guide to gynecologist, neonatologist, cardiologist, and neuroradiologist.

BACKGROUND

Vein of Galen malformations (VGMs) also known as Vein of Galen aneurysmal malformations (VGAMs) are extremely rare congenital arteriovenous malformation involving the intracranial vessels. VGMs incidence is 1:10’000–25’000 accounting for less than 1% of all intracranial vascular malformations[1, 2]. However, in fetal and pediatric populations VGM represents the most common intracranial vascular anomaly accounting for 30% of all endocranial vascular malformations[1–3].

VGM involves multiple arteriovenous shunts draining into a dilated vein called prosencephalic vein of Markowski (MProsV), that normally disappears during embryogenesis and represents the precursor of the Galen’s vein. During the neurogenesis, in the choroidal stage, between the 6th and the 11th week, the choroid plexus supplies the developing brain and MProsV represents the main draining vessel. Later on, with the development of the main cortical arterials and cerebral veins, the choroidal arteries and the
anterior part of MProsV disappear with its posterior segment forming Galen's vein. The genesis of VGAM comes from an anomaly of this process, the anterior part of MProsV doesn't disappear but enlarges due to the high pressure of the choroidal feeders forming the vascular malformation [2–6].

According to the Lasjaunias classification, VGMs can be divided into choroidal type and mural type[5, 7].

The choroidal type is the most frequent and more severe one: multiple feeding arteries form a nidus before entering in the anterior part of MProV. The mural type is characterized by single or multiple fistulas that drain directly into the wall of MProV[7].

In this manuscript we conducted a retrospective study performing a literature systematic review. Our study aimed to study the role of prenatal diagnosis of VGMs, prenatal predictive features and to define the best prenatal and postnatal approach and management.

**METHODS**

We conducted a systematic review in PUBMED and EMBASE from the 1st January 2003 to the 1st January 2023 using the following keywords: fetal vein of Galen aneurysmal malformation, fetal VGAM, arteriovenous malformation of Galen vein, fetal Vein of Galen malformation, prenatal diagnosis). We searched for papers describing prenatally diagnosed VGM. Only case reports and case series were included. 178 articles were selected. Data extraction from individual studies was performed in triplicate. After reading titles, and abstracts, and eliminating duplicates 29 papers were selected and assessed by the authors (Fig. 1). We assessed the gestational age (GA) at diagnosis, the presence of prenatal hydrocephalus, cardiomegaly, associated anomalies, the pregnancy outcome, birth and postnatal outcome. In each included paper we evaluated all variables. For each variable, we reported the total of cases in which that variable was available; when a variable was not described, it was considered as “not valuable”. All data were collected in a dedicated database and analyzed by a statistician using SPSS for Windows (SPSSInc., version 23.0, Chicago, IL). Categorical data were presented with numbers and percentages, and continuous data were reported as mean/median and range, according to the statistical distribution.

**RESULTS**

Twenty-nine papers reporting a total of 50 cases were included [8–37]. All pregnancies were singleton except one twin pregnancy. Data regarding prenatal and birth outcome are depicted in Table 1. The diagnosis was performed around the 31th week of GA (22–37). Fetal hydrocephalus was present in 40% (20/50), cardiomegaly in 58% (29/50), and fetal heart failure was present in 65,51% (19/29) of fetuses with cardiomegaly. Fetal MRI was performed in 61,90% (26/42) of cases. Associated anomalies were: two polyhydramnios, one oligohydramnios, one VACTREL syndrome, one recurrent hydrothorax, and one adrenal hemorrhage. We have post-natal data of 42 VGAM cases (4 cases opted for voluntary interruption of pregnancy, in 4 cases no data regarding the post-natal care was present). Median GA at birth was 38
weeks (28–41). Postnatal outcome are depicted in Table 2. 21.42% (9/42) were discharged home in stable condition with the indication of elective embolization at 5 months. Of them, 3 received elective embolization, in two cases the embolization was successful and uneventful, in one case embolization was complicated by secondary hemorrhage and the patient developed hemiparesis. 1/9 experienced a spontaneous thrombosis, 2/9 developed hydrocephalus and seizure at three months, and 1/9 hydrocephalus a 2 months so urgent embolization was performed with full recovery. 2/9 were still waiting for the elective embolization. 78.53% (33/42) were admitted to the neonatal intensive care unit (NICU), and the median day of admission was the first day of life (1–15). Heart failure was the main cause of NICU admission (Table 2). All of them received cardiovascular therapy. Of them 20 died and the conditions were too severe to perform embolization, median day of death was four days. In 12 cases urgent embolization was performed and 7 patients survived after the procedure. In one case embolization was not performed and the patient survived with severe neurocognitive development. A ventricle-peritoneal shunt was positioned in four patients. The overall mortality was 59.52% (25/42). In the survivors group, 76.50% (13/17) had a normal development, 11.75% (2/17) had mild neurological disability and 11.75% (2/18) presented severe neurological disability. Death occurred for heart failure and brain injury. In Table 3 are depicted the difference between fetal features of VGMs patients with favorable outcome (normal or mild cognitive impairment) and unfavorable outcome (exitus or severe cognitive impairment). The presence of prenatal cardiomegaly, heat failure and hydrocephalus is associated with a worst outcome.

**DISCUSSION**

VGM accounts for less than 1% of all intracranial vascular malformations, however, in the fetal and pediatric population represents the most common vascular malformation of the brain [1, 2]. The diagnostic process starts in the fetal life and a multidisciplinary approach is needed to diagnose and treat this condition.

The features of VGMs and its complications are not the same in the fetus and in the newborn. The early diagnosis before birth has multiple benefits: the woman can receive adequate information, a specific post-natal team can be met prenatally and can fully inform the couple and organize the post-natal care.

Prenatal management:

Prenatal diagnosis is achieved in almost 30% of cases [1]. Prenatal diagnosis is usually made during the third trimester. In the sagittal plane, the ultrasound appearance is characterized by a hypoechoic midline tubular structure localized in the posterior part of the third ventricular described as “comet tail” or “keyhole sign”. The Doppler shows turbulent arterial and venous flow [1, 18]. In the coronal plane, VGM appears as a round cystic structure. The differential diagnosis includes arachnoid cyst, porencephaly cyst, choroidal papilloma and brain tumor; the use of color Doppler can easily help to differentiate these conditions [1, 18, 19, 21, 23, 26, 29]. When there is a suspicion of VGM the execution of fetal MRI should be always advised for a better study of the brain anatomy [17, 32, 33].
Hydrocephalus is present in almost 40% of cases and results either from the high venous pressure that interferes with the cerebrospinal fluid (CSF) drainage or due to the compressive effect of the malformation. From our study the presence of prenatal hydrocephalus was associated with a worst outcome [15, 38].

Cardiomegaly is present in almost 60% of cases. The increment of the cardio thorax index is mainly due to the dilatation of the superior vena cava and the right ventricle probably due to the high venous return from the brain [39]. Cardiac involvement is less present in fetal life compared to the post-natal period due to the low vascular resistances of VGM that balanced by the low resistance of the uteroplacental unit [3, 40].

A prenatal neuroradiological, cardiological, and neonatological evaluation should be offered to explain to the pregnant woman the possible complications and the post-natal management. We advise also a genetic consult. A fetal ultrasound with fetal echocardiography should be offered at least every two weeks [3, 39, 40]. The type of birth should be personalized for each case; in the absence of cardiological dysfunction and no other contraindication, vaginal delivery can be performed safely [1]. From our review vaginal delivery was performed in almost one third of cases.

In previous studies, the presence of fetal cardiomegaly and ventriculomegaly were associated with poor outcome [3, 39, 41, 42]. Our prenatal data are overlapping with previous studies. In our review the presence of prenatal cardiomegaly, heart failure and hydrocephalus was associated with a worst postnatal outcome and none of the newborns that were discharged home with elective embolization presented these conditions prenatally. In presence of these features we recommend to deliver the newborn in a full equipped center.

Postnatal management:

At birth and during the first hours/days of life patients with VGMs usually present good and stable conditions, however, the instability can be developed in hours/days mainly due to the change from the fetal to the postnatal circulation. These newborns should be assisted or rapidly transfer to a specific center where a neuroradiologist, neonatologist, pediatric cardiologist, and neurosurgeon are present [42].

Embolization is the main treatment, the approach can be transarterial or transvenous, however, the transarterial close with polymeric glue is the most used one. The transvenous approach is less effective and has a higher risk of complication[31, 43, 44]. Usually, more than one procedure is needed to achieve the occlusion of VGAM since the amount of parenteral fluid and contrast is limited in newborns and infants [11]. The main goals of embolization are reducing the cardiovascular stress and the brain high pressure to favor CSF drainage and allowing the normal development of the brain. The time of the embolization is depicted by the cardiac hemodynamic and the brain involvement. [11, 42–44].

Lajaunias has proposed The Bicetre score that values the cardiological, neurological, hepatic, renal, and respiratory function; If the score is < 8, the condition is too severe to undergo embolization, between 8 and
12 the patient is a candidate for urgent treatment, if > 12 elective treatment at at least 5 months old should be proposed [42, 45]. In our review the outcome was negative in newborns that were not eligible for embolization; on the other hand more than half newborns who underwent embolization survived with a good odds of normal development or mild disability.

In the case of hemodynamic and brain stability, pediatric assessment should be performed at least every two weeks with a stable assessment of head circumstances, and head CT or MRI should be performed at 4, 8, 16 ad 24 weeks [44]. Embolization is usually performed around the 5th months [42, 44]. This occurs in only 20% of prenatal-diagnosed VGMs.

Almost 80% of VGM newborns tend to present cardiac insufficiency during the first days of life and hemodynamic instability is the main cause of death. The lowering of pulmonary circle pressure and the closing of PDA increase systemic vascular resistance and can trigger cardiac insufficiency. The genesis is due to the volume and pressure overload in the right chambers. For the low vascular resistance in the head, the majority of the ejection fraction is directed toward the brain (STEAL effect of VGM) [39]. This phenomenon can cause lactic acidosis and may cause also cardiac and systemic ischemia. Pulmonary hypertension can be present mainly due to the volume overload in pulmonary arteries [39, 46]. On echocardiography the heart is structurally normal however there is cardiomegaly, the right chambers appear dilated and hypokinetic while the left chambers are hyperdynamic. Cardiological treatment usually involves diuretics and volume restriction to reduce the preload and vasoactive agents [40, 46–48]. The pediatric cardiologist plays a main role in VGM management and during hospitalization, especially after the embolization, a daily assessment is mandatory.

Outcome

From our review the overall mortality of prenatal-diagnosed VGM was almost 60%, however favorable neurological development was achieved in the majority of survivors. Our results are in line with previous studies [3, 29, 41, 42].

Genetic:

In the genetic era all VGM patients should receive a genetic evaluation.

Mutations in RASA1, ENG,ACVRL1, ALK1, SMAD4 have been associated with genetic VGM, with RASA1 being the most frequent one [2, 49, 50].

CONCLUSION

Our study provides data regarding the prenatal main characteristics of VGMs and provides information regarding prenatal, birth, and post-natal management. To be best of our knowledge, this is the largest review conducted to date. We highlight the need to personalize the management based
on the neurological and cardiological status. The limitation of our study is the small sample size mainly due to the rarity of the disease and that the data are extracted from different manuscripts where the authors work with different equipment and different medical possibilities.

We aimed to offer the gynecologist, neonatologist, cardiologist, and neuroradiologist a uniform guide.

**List Of Abbreviations**

VGMs Vein of Galen malformations

VGAMs Vein of Galen aneurysmal malformations

MProsV Prosencephalic vein of Markowski

GA Gestational age

NICU Neonatal intensive care unit

CSF Cerebrospinal fluid

IVG Voluntary interruption of pregnancy

NDD Neurodevelopmental delay

**Declarations**

Ethics approval and consent to participate: not applicable

Consent for publication: not applicable

Availability of data and materials: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

Funding: The authors declare that no funding was used

Authors' contributions: CS, LLM and ADM ideated the manuscript, LDM, GS and PT wrote the original draft. GO and LDM reviewed critically the manuscript and edited the final draft. All authors approved the final version.

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**References**


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Tables
<table>
<thead>
<tr>
<th>Variable (N)</th>
<th>Variable subclassification</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA at presentation (N = 49)</td>
<td></td>
<td>31 week (22–37)</td>
</tr>
<tr>
<td>IVG (N = 50)</td>
<td></td>
<td>8% (4/50)</td>
</tr>
<tr>
<td>Prenatal hydrocephalus (N = 50)</td>
<td></td>
<td>40% (20/50)</td>
</tr>
<tr>
<td>Cardiomegaly (N = 50)</td>
<td></td>
<td>58% (29/50)</td>
</tr>
<tr>
<td>Fetal heart failure (N = 50)</td>
<td></td>
<td>38% (19/50)</td>
</tr>
<tr>
<td>MRI in utero (N = 42)</td>
<td></td>
<td>61,90% (26/42)</td>
</tr>
<tr>
<td>GA at birth (N = 42)</td>
<td></td>
<td>38 week (28–41)</td>
</tr>
<tr>
<td></td>
<td>Extremely preterm</td>
<td>4,76% (2/42)</td>
</tr>
<tr>
<td></td>
<td>Very preterm</td>
<td>2,40% (1/42)</td>
</tr>
<tr>
<td></td>
<td>Preterm</td>
<td>21,42% (9/42)</td>
</tr>
<tr>
<td></td>
<td>At term</td>
<td>71,42% (30/42)</td>
</tr>
<tr>
<td>Mode of delivery (N = 34)</td>
<td>Cesarian section</td>
<td>67,64% (23/34)</td>
</tr>
<tr>
<td></td>
<td>Vaginal delivery</td>
<td>29,41% (10/34)</td>
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<tr>
<td></td>
<td>Operative delivery</td>
<td>2,95% (1/34)</td>
</tr>
<tr>
<td>APGAR SCORE (N = 28)</td>
<td>APGAR 10’ 7–10 (N = 28)</td>
<td>75% (21/28)</td>
</tr>
<tr>
<td></td>
<td>APGAR 10’ 4–6 (N = 28)</td>
<td>25% (7/28)</td>
</tr>
<tr>
<td></td>
<td>APGAR 10’ 0–4 (N = 28)</td>
<td>0% (0/28)</td>
</tr>
</tbody>
</table>

*GA: gestational age; IVG: voluntary interruption of pregnancy*
<table>
<thead>
<tr>
<th>Variable (N=)</th>
<th>Variable subclassification</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns with VGM (N = 42)</td>
<td>Discharged home with elective embolization</td>
<td>21.42% (9/42)</td>
</tr>
<tr>
<td></td>
<td>Admission to NICU</td>
<td>78.53% (33/42)</td>
</tr>
<tr>
<td>Main complication for NICU admission</td>
<td>Heart failure</td>
<td>88.88% (29/33)</td>
</tr>
<tr>
<td>N = 33</td>
<td>Hydrocephalus</td>
<td>3.03% (1/33)</td>
</tr>
<tr>
<td></td>
<td>Respiratory distress</td>
<td>6.06% (2/33)</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td>3.03% (1/34)</td>
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<tr>
<td>Day of admission to NICU (N = 28)</td>
<td>1 day of life (1–15)</td>
<td></td>
</tr>
<tr>
<td>Outcome in NICU (N = 33)</td>
<td>Embolization</td>
<td>Exitus</td>
</tr>
<tr>
<td>(N = 12)</td>
<td></td>
<td>36.36% (12/33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>41.66% (5/12)</td>
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<tr>
<td></td>
<td></td>
<td>Survivors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>58.34% (7/12)</td>
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<tr>
<td></td>
<td>Medical therapy</td>
<td>Exitus</td>
</tr>
<tr>
<td>(N = 21)</td>
<td></td>
<td>63.64% (21/33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95.23% (20/21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Survivors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.77% (1/21)</td>
</tr>
<tr>
<td>Outcome of newborns discharged home with elective embolization (N = 9)</td>
<td>Waiting for elective embolization</td>
<td>22.2% (2/9)</td>
</tr>
<tr>
<td></td>
<td>Spontaneous thrombosis</td>
<td>11.1% (1/9)</td>
</tr>
<tr>
<td></td>
<td>Emergent embolization</td>
<td>33.35% (3/9)</td>
</tr>
<tr>
<td></td>
<td>Elective embolization</td>
<td>33.35% (3/9)</td>
</tr>
<tr>
<td>Outcome of VGM newborns (N = 42)</td>
<td>Exitus</td>
<td>59.52% (25/42)</td>
</tr>
<tr>
<td></td>
<td>Survivors</td>
<td>40.48% (17/42)</td>
</tr>
<tr>
<td>Day of death (n = 18)</td>
<td>4 day of life (1–26)</td>
<td></td>
</tr>
<tr>
<td>Outcome of survivors (N = 17)</td>
<td>Normal neurodevelopment</td>
<td>76.50% (13/17)</td>
</tr>
<tr>
<td></td>
<td>Mild NDD</td>
<td>11.75% (2/17)</td>
</tr>
<tr>
<td></td>
<td>Severe NDD</td>
<td>11.75% (2/17)</td>
</tr>
</tbody>
</table>

VGM: vein of Galen malformation, NICU: neonatal intensive care unit; NDD: Neurodevelopmental delay
Table 3
PRENATAL FEATURES IN GOOD AND POOR POST-NATAL OUTCOME

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors with none or mild NDD</th>
<th>Exitus or severe NDD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N:15</td>
<td>N:27</td>
<td></td>
</tr>
<tr>
<td>Mean GA at diagnosis</td>
<td>33</td>
<td>32</td>
<td>0.19</td>
</tr>
<tr>
<td>Prenatal cardiomegaly</td>
<td>4/15</td>
<td>18/27</td>
<td>0.012*</td>
</tr>
<tr>
<td>Prenatal Heart failure</td>
<td>2/15</td>
<td>14/27</td>
<td>0.013*</td>
</tr>
<tr>
<td>Prenatal hydrocephalus</td>
<td>0/15</td>
<td>13/27</td>
<td>0.004**</td>
</tr>
</tbody>
</table>

GA: gestational age, NDD: Neurodevelopmental delay

Figures
Figure 1

PRISMA CHART

Identification of studies via databases and registers

Identification

Records identified from EMBASE and PUBMED (n=178)

Records removed before screening:
Duplicate records removed (n =32 )

Screening

Records screened (n = 146)

Records excluded (n =80 )

Reports assessed for eligibility (n =66 )

Reports excluded: (n =37 )

Included

Studies included in review (n =29)