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Severe cardiac failure in newborns with VGAM

Prognosis significance of hemodynamic parameters in neonates presenting with severe heart failure owing to vein of Galen arteriovenous malformation

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Abstract *Objective:* Neonatal vein of Galen malformation complicated by severe cardiac failure is a rare disease. The purpose was to assess the outcome of this life-threatening malformation and identify hemodynamic prognostic factors.
Design: Retrospective study.
Patients: Twenty-four newborns with cardiac failure requiring mechanical ventilation were consecutively admitted from 1986 to 2000.
Interventions: Cardiovascular evaluation including echocardiogram was performed in all cases. Eighteen transarterial shunt occlusions with glue were applied by the same team of three physicians. *Measurements and results:* Twelve babies survived and underwent one endovascular session at least (median age 20 days) with a mean 63 months follow-up. Embolization was not performed in 6 of the 12 nonsurvivors because of severe brain damage or profound hypotension Cardiogenic shock occurred in all nonsurvivors, but also in one long-term survivor (p<0.0001). Echocardiogram showed signs of right ventricular failure, most often in the dead babies (p=0.005). The pulmonary systemic arterial pressure ratio was significantly higher in the nonsurvivor group (p=0.031), and it decreased significantly after the first embolization only in patients who survived (p=0.01). Patent ductus arteriosus and a diastolic aortic reversed-flow were present in all nonsurvivors in contrast to 30% of the long-term survivors (p=0.003). There was no difference in the left ventricular contractility and mean cardiac output between the two groups.
Conclusions: The outcome of vein of Galen malformation complicated by severe cardiac failure requiring mechanical ventilation remains poor. Neonatal embolization seems to be beneficial only in babies without suprasystemic pulmonary hypertension.

Keywords Newborn · Severe cardiac failure · Vein of Galen malformation · Persistent pulmonary hypertension of the newborn · Encephalomalacia · Ductus arteriosus · Embolization

Introduction

Vein of Galen aneurysmal malformation (VGAM) is a rare but potentially life-threatening cerebral vascular malformation. It was the first cerebrovascular malformation recognized to be of embryonic origin. It develops from the median vein of the prosencephalon [1]. Symptoms may vary, depending on the patient's age. There is congestive heart failure and encephalomalacia in neonates, macrocrania and hydrocephalus in infants and minimal cardiac insufficiency, asymptomatic cardiac enlargement, headaches, or intracranial hemorrhage in older children. Neurodevelopmental delay or convulsions may occur at any age, but with different mechanisms and pathophysiology [1].

First described by Gold et al., VGAM revealed by severe cardiac failure remains a rare neonatal disease, often having a fatal outcome or complicated by severe brain damage [2, 3]. Since the introduction of transarterial endovascular occlusive procedure with glue, the survival rate and incidence of neurologic complications have significantly improved over the last 15 years [1, 4]. The improvement in fetal and postnatal ultrasound techniques allows an earlier diagnosis of VGAM and prompt management of these patients. This has encouraged neonatologists to refer neonates with severe cardiac failure to an interventional neuroradiology team earlier than in the past [5]. However, there is still controversy as to the ideal timing of endovascular management. In this study, we assessed the outcome and evaluated the hemodynamic profile of neonates with VGAM complicated by severe cardiac failure in order to identify possible prognostic factors.

Material and methods

From October 1986 to June 2000, 258 patients with VGAM were hospitalized at our institution for evaluation and treatment. Data were analyzed retrospectively, using the patient's chart, following a database system. The analysis was limited to a group of newborns with proven VGAM, who were admitted to the pediatric intensive care unit (PICU) with severe cardiac failure requiring mechanical ventilation. Severe cardiac failure was defined clinically by the presence of tachycardia, respiratory distress, and hepatomegaly. Cardiogenic shock was defined by the presence of clinically poor peripheral perfusion, oliguria and the need for inotropic support, independently of the level of systemic arterial blood pressure or biochemical markers of organ failure. The neurologic evaluation included a physical examination, EEG, CT scan and MRI. Laboratory tests included arterial blood gases, PT and PTT, CBC with platelet count, plasma lactate level, and liver and renal function tests to assess the presence of peripheral organ injury (data not shown).

A cardiac ultrasound evaluation was performed in every patient at the time of admission and repeated a few days after each endovascular procedure. It included the measurement of the right and left end-diastolic diameters (RVEDD, LVEDD), left ventricular shortening fraction (LVSF), stroke volume (SV), left ventricular output (reflecting cardiac output or CO as the product of velocity time integral by the cross-sectionnal area at the aortic valve level and multiplied by the heart rate), and systolic pulmonary arterial pressure, based on measurement of the tricuspid flow regurgitation with the modified Bernouilli equation. Cardiac malformations were ruled out as well as the presence of a patent ductus arteriosus (PDA) and a patent foramen ovale (PFO). The ductal flow pattern were analyzed according to pulsed Doppler sampling placed in the color area of the highest velocity. Descending aortic flow reversal was researched at the level of the PDA insertion. The shape of the interventricular septum was described, based on the right-to-left side motion, as: 1=normal, 2=intermediate, and 3=complete right-to-left shift with LV collapse.

The presence of brain damage or encephalomalacia was considered to be a contraindication for the endovascular procedure, and the patient's eligibility for this procedure was based upon our previous results [1, 6, 7]. Conversely, when cardiac function improved following the initial management, the embolization procedure was postponed until the baby was 5 months old. The endovascular procedure consisted in catheterization of the femoral artery and a first transarterial occlusion session using *N*-butyl cyanoacrylate. The goal for this first session was to reduce the shunt by a third, based on the size of the aneurysm [8].

Patients were divided into two groups based on outcome: survivors and non-survivors. Fisher's exact test and Wilcoxon rank-sum test were used for statistical analysis. A $p<0.05$ was considered significant.

Results

Ninety-six newborns diagnosed with VGAM were hospitalized at the Bicêtre Hospital between October 1986 and June 2000. Twenty-four of them (25%), including 19 who were hospitalized after 1992, were admitted to the PICU because of cardiac failure and the need for mechanical ventilation. Fifteen were male, and the median postconceptional age was 40 weeks. Twelve patients died during hospitalization (including 1 before 1992) (non-survivor group, NS). Six of them were not embolized because of impossible technical challenges (severe cardiogenic shock with hypotension and aortic reverse flow, $n=3$) or evidence of severe brain damage ($n=3$) and died. Six more patients died after the first embolization because of multiple organ failure and intractable cardiac failure. Twelve patients (50%) underwent a first successful embolization of the VGAM and were then discharged (survivor group, S). There was no difference between the S and NS groups with respect to postconceptional age, sex, birth weight, and head circumference (Table 1). The procedure was done at 21 (7–38) days of life with no difference between the S and NS groups (26 vs 20 days, respectively, p=ns). The diagnosis of VGAM was made in utero by fetal ultrasound in three babies by the third trimester of pregnancy. Two of them also had a fetal MRI. The median age at the time of VGAM diagnosis in the remaining 21 babies was 3 days (0–15) with no differences between the S and NS group (Table 1). There was also no difference with respect to the time of appearance of clinical signs of cardiac failure and the beginning of mechanical ventilation between the two groups (Table 1).

All babies presented clinical signs of severe cardiac failure at the time of admission, with tachycardia, tachypnea, and hepatomegaly. Most of them had a cervical "dancing" carotid pulse and distended jugular veins. Every patient presented a peripheral pulse and precordium bounding owing to a hyperdynamic status with increased venous return and right heart overload at the echocardiogram (Table 2). The initial treatment consisted of continuous enteral feeding, a diuretic (furosemide 2–6 mg/kg per day) to reduce the preload and mechanical ventilation. Every patient received opioids and benzodiazepines to lower oxygen consumption. The hemodynamic management was then based on the echocardiogram findings. An infusion of dobutamine was started in 13 patients because of normal- to low-cardiac output, poor peripheral perfusion, and/or low urinary output and severe right cardiac failure. Seven patients received additional dopa-

Table 1 Clinical characteristics of newborns with VGAM and severe cardiac failure. Results are expressed as percentage or median (range) as appropriate. Fischer's exact test and Wilcoxon rank-sun test are used for statistical analysis (*VGAM* vein of galen malformation, *MV* mechanical ventilation, *CCF* clinical cardiac failure)

	All newborns	Dead	Survival	*p*
n (before 1993)	24 (5)	12 (1)	12 (4)	
Sex ratio F (%)	37.5	42	33.3	1
Gestational age (weeks)	40 (36–42.7)	40 (36.7–41)	39 (36–42.7)]	0.58
Birth weight (percentile)	75th	77.5th	75th	1
Head circumference (>95th percentile)	50%	50%	50%	1
VGAM diagnosis (days of life)	2.5 (0–15)	1.5 (0–15)	3 (0–8)	0.1
CCF diagnosis (days of life)	1.5 (0–14)	2 (0–14)	1 (0–5)	0.2
MV onset (days of life)	3 (0–19)	2.5 (1–19)	3 (0–17)	0.47
PICU admission (days of life)	12 (0–25)	12 (2–22)	11.5 (0–25)	0.56
Inotropic drug use	13	12	1	<0.0001
Dobutamine	6	5	1	
Dobutamine+ dopamine	7	7		
Endovascular treatment				
Yes	18	6	12	0.014
First session (days)	21 (7–38)	20 (11–29)	26 (7–38)	0.68
Neurological outcome				
Developmental delay			9	
Epilepsy			3	

Table 2 Cardiac parameters before the first endovascular embolization of the VGAM (*LVSF* left ventricular shortening fraction, *LVEDD* left ventricular end-diastolic diameter, *RVEDD* right ventricular end-diastolic diameter, *SIV* shape of the interventricular septum, *PDA* patent ductus arteriosus). The SIV was based on the right-to-left side motion as follows: 1=normal, 2=intermediate, and 3=complete right-to-left shift with LV collapse

Ultrasound parameters	Dead (*n*=12)	Survival (*n*=12)	*p*
PDA (right-to-left shunting %)	10 (80%)	4 (25%)	0.003
LVEDD (mm)	20 (10–23)	20 (15–27)	0.23
LVSF (%)	47 (30–55)	39.5 (31–53)	0.68
RVEDD (mm)	16 (11–25)	15.5 (8–18)	0.82
SIV pattern 1/2/3 (*n*=)	0/2/8	4/3/2	0.005
Cardiac output (ml:min.kg^{-1})	395.5(265–650)	325.5 (224–500)	0.29
Systemic arterial pulmonary pressure (mmHg)	67.5 (44–85)	65 (40–90)	0.19
Suprasystemic arterial Pulmonary pressure (%)	70%	20%	0.031
Descending aortic diastolic reverse flow (*n*=)	8	1	0.0007

mine because of refractory hypotension (see Table 2). Inhaled nitric oxide challenge failed to demonstrate any right pulmonary arterial pressure decrease or right ventricular discharge in two (one in each of the two groups). Three were infused with PGE2 to maintain the open ductus arteriosus and lower the right ventricle after-load with success (including one patient in the S group).

Every patient in the NS group suffered from cardiogenic shock as previously defined, compared with only 1 patient in the S group (8.3%) ($p<0.0001$). Based on the ventricular septum right-to-left side motion, signs of right ventricular failure and reduced left ventricular preload (SIV pattern=3) were more common in the NS group ($p=0.005$) (Fig. 1, Table 2). The pulmonary artery pressure (PAP) was similar in both groups (Table 2). However, the systemic pressure (SAP) was significantly lower in the NS group, and the ratio pulmonary over systemic arterial pressure was significantly higher in the NS group (Table 2, $p=0.031$). The incidence of PDA with right-to-left shunt and diastolic descending aortic reverse flow was significantly higher in the NS compared to the S patients (80 vs 25%, $p=0.003$). LVSF and CO were similar in both groups (Table 2).

Embolization was performed in half of the NS patients and in all the 12 S patients. The LVEDD, LVSF, CO did not change after embolization in either group. We observed a significant decrease of the PAP (–32%, $p<0.01$) in the S group after embolization, with a normalization of the PAP/SAP ratio (data not shown). However, PAP increased significantly (+25%, $p<0.04$) after embolization in the NS group. The right-to-left shunt disappeared after embolization in the S patients, while it increased significantly in the NS patients. The RVEDD also increased significantly by 37% in the NS patients after embolization ($p<0.03$).

Mechanical ventilation was stopped on average 5 days after the embolization in the S patients. The median follow-up in these patients was 63 months. Thereafter, all babies received diuretics and/or digoxin. None of them developed further episodes of cardiac failure. Four in-

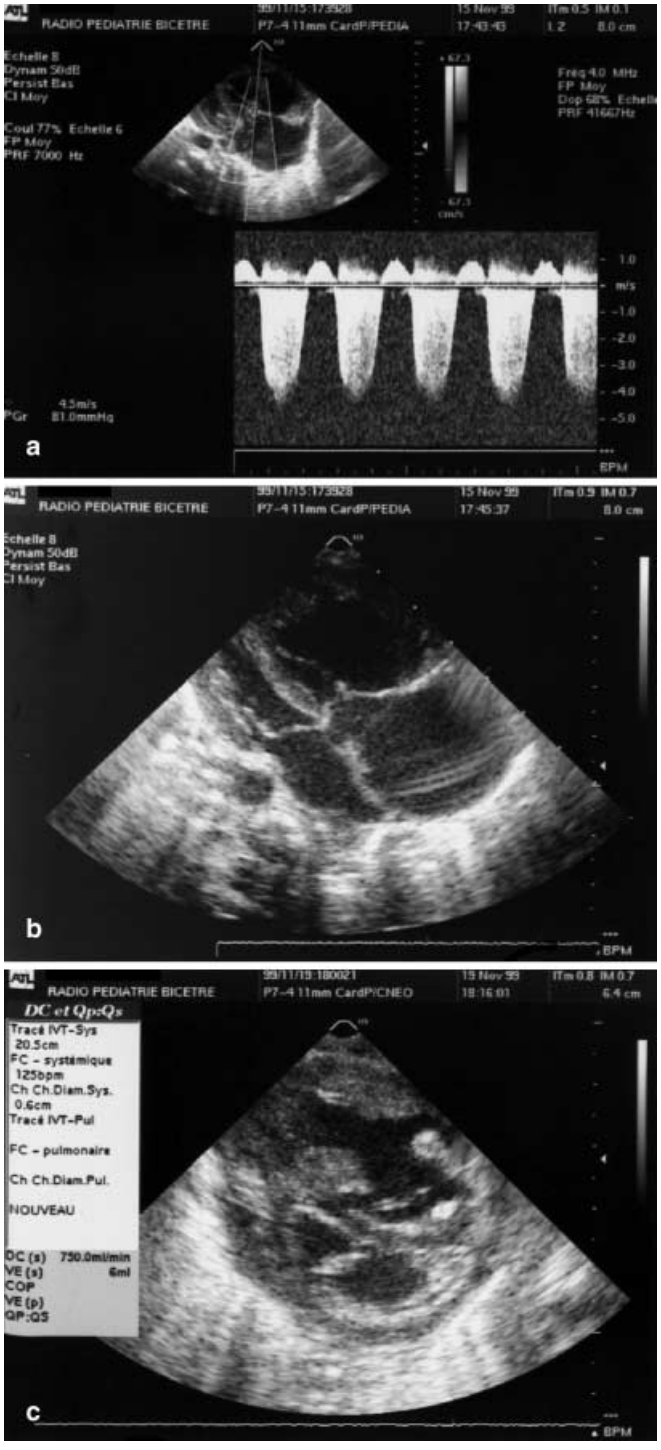

Fig. 1 Example of right cardiac failure and PPHN complicated VGAM in a neonate (4-D echoviews). **a** Suprasystemic arterial pulmonary hypertension level on the tricuspid flow regurgitation estimated to be around 90 mmHg. **b** Right cardiac failure. *Right cardiac chambers. **c** Type 3 septum ventricular pattern in the same patient

fants were followed less than 24 months: three of them had normal neurologic findings, and only one showed neurodevelopmental delay (based on the Denver scale of infant development) with axial hypotonia. At least 24 months of follow-up were available in the others. Three of them had a moderate neurologic delay, including seizures in one, but without severe neuromotor or cognitive deficits (sociability and school attendance). Five were classified as having a severe disability in the sensory and communication domain, including two seizures, without having the opportunity to attend regular school. All of them had neuromotor sequelae.

Discussion

We report our experience in the management of 24 babies consecutively admitted with true VGAM and severe cardiac failure requiring mechanical ventilation during the neonatal period. This study seems to confirm, as previously reported, that neonatal VGAM complicated by severe cardiac failure has a poor outcome, with a 50% early mortality [2, 3]. An analysis of several hemodynamic and cardiac parameters showed that the presence of severe suprasystemic pulmonary artery hypertension, cardiogenic shock, PDA with a significant right-to-left shunt, and a descending aortic diastolic reverse flow before embolization is indicative of poor prognosis. These hemodynamic parameters, mimicking fetal persistent circulation, are indicative of poor prognosis markers for the disease [9]. Such persistence of a fetal type of circulation should not be regarded as a true anomaly despite some unusual reports of associated congenital cardiac abnormalities (e.g., sinus venosus atrial septal defects, and aortic coarctation) [10]. An interesting finding in this study was that a successful embolization with at least 30% reduction of the intracerebral arteriovenous shunt does not always affect the PAP, which only significantly decreased in the S patients. Moreover, the neurologic outcome in the patients who survived beyond the first embolization was also severe, because only one quarter of them had normal neurologic development in the follow-up period. None of the NS patients in our series was suspected antenatally to have cardiac abnormalities, which may reflect a selection bias since fetal cardiac failure (e.g., antenatal heart dilation) has already been recognized as a situation with irreversible brain damage [7].

The systemic hemodynamic profile for VGAM in neonates has been previously documented with primary cardiac catheterization and Doppler color ultrasound studies in the few cases reported [11, 12, 13]. The high-flow arteriovenous shunt leads to a dramatically increased systemic venous return throughout a dilated superior vena cava and enlarged right cardiac chambers. The high pulmonary blood flow contributed to the left cardiac chambers overload and high CO. The increased PAP prevents the closure of the ductus arteriosus, with a subsequent right-to-left

shunt. The retrograde aortic flow into the arch arteries adds to the reduced cerebral blood flow [11, 13]. In the most severe situation, systolic right ventricular and pulmonary arterial pressure is superior to the systemic arterial pressure, and this leads to the intractable cardiac and multiple organ failure (the ventricular septum right shift reduced both the end-diastolic left ventricular preload and cardiac output) [14, 15]. Moreover, sometimes reduced coronary diastolic pressure gradient led to ischemic myocardial damage, as previously suspected by ECG recording or documented by pathologic features in various cerebral vascular malformations [16]. We speculate that in this earlier right or biventricular cardiac failure (e.g,. symptomatic cardiac failure requiring MV during the first week of life) there is a fixed arterial pulmonary vascular resistance that cannot be reversed by embolization of the VGAM or by inhaled nitric oxide. However, such inefficient treatment represents 4.5% of the overall VGAM referred.

There are several experimental data showing that increased pulmonary blood flow and pulmonary hypertension can alter the normal postnatal vascular remodeling, preventing a fall in pulmonary vascular resistance, even once the cause of the pulmonary overflow is removed [17]. A recent PPHN fetal model with high pulmonary blood flow, obtained by aortopulmonary shunt placement, provided convincing data for an alteration of the endothelin cascade by earlier upregulation of gene expression, contributing to vascular remodeling and enhancement of pulmonary vascular reactivity [18].

In conclusion, the outcome of VGAM complicated by cardiac failure is poor, despite early diagnosis and prompt management. Only neonates with subsystemic arterial pulmonary pressures seem to benefit from early embolization. Further studies are needed to understand better why successful embolization can improve systemic hemodynamics in only a fraction of these patients. Within the limit of our retrospective study, earlier embolization procedure should be considered cautiously with regard to the high mortality or poor neurologic outcome.

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