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THÈSE POUR LE DIPLÔME D'ÉTAT

DE DOCTEUR EN MÉDECINE

Un syndrome inflammatoire systémique est associé à la survenue D'une hypertension pulmonaire dans une population d'enfant Porteurs d'omphalocèles géantes

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Au Pôle Formation

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Liste des abréviations

GO Giant omphalocele

HTP Hypertension Pulmonaire

PH Pulmonary hypertension

CDH Congenital diaphragmatic hernia

CRP C reactive protein

Introduction

L'omphalocèle est une anomalie relativement commune avec une incidence d'environ 1 sur 6000 naissances vivantes [1]. C'est un défect abdominal antérieur où on observe une hernie de la paroi ventrale avec protrusion des organes abdominaux entourés d'un sac protecteur composé de péritoine, de tissu conjonctif mésenchymateux et d'amnion.

Il existe des anomalies du caryotype associées dans environ 50% des cas et des malformations jusque dans 70% des cas [2]. Les trisomies 13 et 18 sont les anomalies les plus fréquentes. Ces malformations peuvent s'intégrer dans un syndrome comme le syndrome de Beckwith-Wiedemann ou la pentalogie de Cantrell associant notamment omphalocèle, hernie diaphragmatique, anomalie sternale, malformation et ectopie cardiaque. On retrouve également des hyper-échogénicités digestives, des scolioses thoraciques et des malformations vasculaires comme l'artère ombilicale unique [3]

Physiopathologie

D'un point de vue embryologique, durant la 3^{e} semaine de gestation, les cavités péricardique, pleurale et péritonéale commencent à apparaitre. La paroi abdominale se forme vers la 5^{e} semaine de gestation et on observe une hernie physiologique de l'intestin régressant à la 9^{e} semaine. Bien que des hernies embryonnaires physiologiques intestinales ont été décrites, elles ne contiennent cependant jamais le foie. De nombreuses théories ont été proposées pour expliquer la genèse de cette anomalie : Arrêt du développement de la cavité abdominale entre la 8^{e} et 12^{e} semaine selon Gross [4] , défaut d'union du septum du mésoderme transverse avec la cavité amiotique, un défaut de réintégration de la hernie physiologique, une dysplasie embryonnaire, ou encore une anomalie des placodes ectodermales. [4–7]

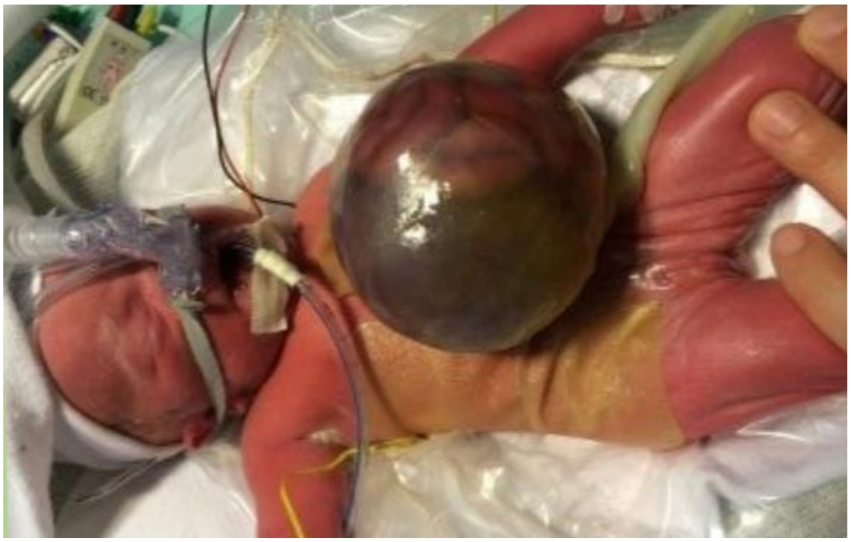

Figure 1 : exemple d'omphalocèle géante

Omphalocèle géante

Parmi les omphalocèles, une forme clinique particulière, généralement définie comme contenant une grande partie du foie, est nommée omphalocèle géante *(voir figure1) [6]*. Une de ces particularités est que l'omphalocèle géante est 4 fois moins associée à des anomalies chromosomiques comparé aux omphalocèles simples, et présente une morbidité, une mortalité et une prise en charge très spécifique [8]. De plus, l'omphalocèle est classiquement décrite comme une coelosomie moyenne, cependant le défect dans le cas de l'omphalocèle géante, est généralement plus haut situé, au niveau ombilical et sus-ombilical, faisant de cette pathologie une entité particulière.

Prise en charge

Plusieurs techniques existent afin de traiter ces omphalocèles géantes, le traitement consistant en la réintégration des viscères en intra abdominal. Les options comprennent un traitement chirurgical d'emblée avec fermeture de la paroi, avec ou sans plaque, ou bien un traitement médical ayant pour but d'épithélialiser la membrane et réaliser une réintégration progressive des viscères avant une fermeture chirurgicale

dans un second temps, habituellement à l'âge de la marche [6]. Parmi les techniques médicales, aucune ne fait consensus. On peut citer le recouvrement cutané selon Gross [4], la technique du silo de Schuster [9], ou la technique de Grob via l'utilisation de topiques [10].

Ces techniques médicales comprennent un risque de sepsis et de rupture du sac, tandis que les traitements chirurgicaux peuvent entrainer des complications respiratoires et abdominales.

Pronostic :

Il a été démontré que parmi les patients atteint d'omphalocèle géante, plus de 50% développaient des degrés variables de problème moteur, cognitif ou langagier et montraient un retard développemental semblable à d'autres populations à risque comme les prématurés [6,11]. Danzer et al montrent notamment une incidence plus importante de l'hypotonie et environ 10% nécessitent une rééducation à 2 ans.[11] La prévalence de l'autisme était de 13% dans cette même étude, taux similaire à la population d'enfants porteurs de hernie diaphragmatique. La lente acquisition de l'autonomie alimentaire, le reflux gastro œsophagien sont également fréquents dans cette population[3].

Cependant, même isolé, il peut exister un retentissement sur le développement pulmonaire et ce en l'absence d'autre pathologie associée. En effet le taux de mortalité de ces formes géantes est de 10 à 25 % selon les cohortes [3,6,8,12]. Un des facteurs de risque connu étant la rupture des membranes protectrices [13] [14].

Les décès sont liés à des complications respiratoires, digestives ou hémodynamiques. Malgré une amélioration de la survie et du pronostic avec les avancées de la prise en charge chirurgicale et néonatale, la morbidité pulmonaire reste commune dans cette population. Ainsi, la sévérité de l'hypoplasie pulmonaire et de l'hypertension

pulmonaire (HTP) a été considérée comme centrale dans le pronostic des patients porteurs d'omphalocèles géantes [15–18].

Les études antérieures ont montré que les marqueurs de l'hypertension artérielle pulmonaire tels que le rapport des vitesses artérielles pulmonaire et la fraction d'éjection du ventricule droit, étaient augmentés chez les patients porteurs d'omphalocèles géantes évoluant défavorablement. Ces enfants avaient une augmentation du rapport pression artérielle pulmonaire sur pression artérielle systémique et les performances du ventricule droit à la première échocardiographie étaient associées à une augmentation de la mortalité [19].

Au long cours, la fonction pulmonaire des porteurs d'omphalocèles géantes survivants montrait une réduction du volume pulmonaire sans obstruction des voies respiratoires, une hyper-réactivité pulmonaire et une diminution de la compliance [20]. Il a été suggéré que cette insuffisance respiratoire pourrait être liée à une hypoplasie pulmonaire, l'augmentation de la pression intra abdominale, une déformation thoracique, une dysfonction diaphragmatique ou une déformation bronchique. [21,22]

C'est donc actuellement un défi majeur pour les périnéonatologistes, les néonatologistes et les chirurgiens pédiatriques impliqués dans la prise en charge, de pouvoir prédire le pronostic et l'évolution postnatale afin de pourvoir aux parents une information éclairée.

L'hypertension artérielle pulmonaire est considérée comme centrale dans la prédiction d'une évolution défavorable. Les hypothèses concernant les causes de cette HTP sont multiples. Elle pourrait être liée à un lit vasculaire restrictif en rapport avec l'hypoplasie pulmonaire, à une part d'inflammation ou de réactivité vasculaire anormale [23].

Les travaux de l'équipe de Shinkichi Kamata concernant la détection prénatale de l'hypoplasie pulmonaire chez ces patients porteurs d'omphalocèles géantes via l'utilisation de ratio comme le ratio poumon/ thorax (P/T) et le ratio de longueur thorax/tronc (C/T) montraient une diminution significative du ratio P/T chez les patients porteurs d'hypoplasie pulmonaire diagnostiquée en post natal et une augmentation du C/T reflétant l'aspect allongé et rétréci du thorax, fréquemment observé en post-natal. [22]. Des études ont démontré la faisabilité de l'utilisation de l'IRM pulmonaire fœtale afin de pronostiquer le devenir néonatal dans la hernie diaphragmatique congénitale [24–26].

Danzer et al. avaient voulu évaluer le volume pulmonaire en IRM et sa capacité à prédire l'évolution des patients atteints d'omphalocèle géante. Ils ont ainsi démontré qu'un rapport volume pulmonaire observé sur attendu <50 % était prédictif d'une plus mauvaise adaptation à la naissance, d'une ventilation prolongée et une durée d'hospitalisation plus importante. [23] Plus récemment son équipe a montré qu'une hypoplasie pulmonaire était associée à une augmentation de la mortalité, d'autant plus que celle-ci était profonde [27]. Cependant il n'existait pas de lien statistiquement significatif entre hypoplasie pulmonaire et hypertension pulmonaire qui reste un facteur important de morbimortalité dans cette population.

L'objectif de cette étude est donc de déterminer des facteurs pronostiques prénataux et postnataux associés au développement d'une hypertension pulmonaire chez les patients porteurs d'omphalocèles géantes.

Systemic Inflammation Is Associated with Pulmonary Hypertension in Isolated Giant Omphalocele: A Population-Based Study

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Abstract: Our objective is to determine perinatal factors contributing to the development of pulmonary hypertension (PH) in patients with isolated giant omphaloceles (GO). All cases of omphaloceles that underwent prenatal and postnatal care at the University Hospital of Lille between 1996 and 2021 were reviewed. We included all infants with isolated GO, including at least a part of the liver, who were treated by delayed surgical closure. Prenatal and postnatal data were recorded and correlated with postnatal morbidities. We compared outcomes between a group of infants with GO who developed PH and infants with GO with no PH. We identified 120 infants with omphalocele. Fifty isolated GO cases fulfilled the inclusion criteria of our study. The incidence of PH was 30%. We highlighted a prolonged inflammatory state, defined as a CRP superior to 15 mg/L, platelets higher than 500 G/L, and white blood cells higher than 15 G/l for more than 14 days in patients who developed PH. This event occurred in 73% of patients with PH versus 21% of patients without PH ($p < 0.05$). Late-onset infection was not different between the two groups. We speculate that prolonged inflammatory syndrome promotes PH in infants with GO treated with delayed surgical closure.

Keywords: giant omphalocele (GO); newborn infant; delayed surgical closure; inflammatory syndrome; pulmonary hypertension

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1. Introduction

Omphalocele is a congenital disease with a defect of the abdominal wall closure that occurs in 3000 to 10,000 live births [1]. Due to the defect, part of the intra-abdominal organs moves out of the body during the intrauterine growth of the fetus. Giant omphalocele (GO) is a rare form of omphalocele. The most common description of GO refers to a large covered defect of the abdominal wall closure containing at least a part of the liver, even though there is no consensus on its definition [2]. Over recent decades, improvement in neonatal management increased the survival of patients presenting a GO, with a reported survival rate of 90% [3,4]. Surgical primary closure of the defect can be performed in small omphaloceles. Nevertheless, giant omphalocele surgical management is complex as the size of the defect makes it difficult to reach the edges of the defect contour (because of the gap, there is a lack of skin material). In addition, it is life-threatening to push back the sac content into the abdominal area as

this maneuver would significantly increase the intra-abdominal pressure and therefore lead to cardiopulmonary failure [5]. Thus, delayed closure of the abdominal defect has been proposed as alternative care. In this way, the sac is topically treated to allow escharization and growth with little or no manipulation of the sac's contents [3,6].

It is known that GO children experience ongoing medical and surgical morbidities. Gastroesophageal reflux is common in this population, as are impaired musculoskeletal development, neurodevelopmental delays, and nutritional disabilities [2,7–10]. However, the main challenge in neonatal care of GO is pulmonary hypertension (PH), which has been considered the main feature of giant omphalocele-associated adverse outcomes [11–13].

The pathophysiology of PH remains unclear. The main hypothesis implies a multifactorial mechanism, including pulmonary hypoplasia, vascular dystrophy, and aggression of assisted ventilation. Evidence exists in experimental PH that inflammation precedes vascular remodeling, highlighting that altered immunity may promote vascular disease [14,15]. Prenatal prognostic assessment in GO reveals that some neonatal outcomes are associated with pulmonary hypoplasia [4,16]. However, no significant association was found between prenatal lung hypoplasia measured by Magnetic Resonance Imaging (MRI) and PH.

The objective of our study is to determine the perinatal factors associated with the development of pulmonary hypertension in GO patients. Our secondary objective is to describe mortality and morbidities in this population.

2. Population and Methods

We designed a population-based study of patients presenting with omphalocele referred to the University Hospital of Lille between November 1996 and September 2021 for prenatal diagnosis. The national commission of information and liberty (CNIL) approved this study.

We retrospectively reviewed all newborns with omphalocele in the Nord-Pas de Calais (North of France department) area admitted during the neonatal period in our center from 1996 to 2021. Among omphalocele cases, GO was defined as an omphalocele including at least a part of the liver [7]. All cases of prenatally diagnosed isolated giant omphalocele were referred to Lille University Hospital and included in a prospective cohort. Newborn infants with GO were included in the present study if they underwent at least one antenatal sonographic evaluation and if the pregnancy resulted

in a live birth at the referral center. Exclusion criteria included GO patients with associated malformations or genetic syndromes, subjects with insufficient postnatal data, patients treated by primary closure of the septal defect, or patients with a documented plan for palliative care [16].

Data on patients' prenatal follow-up, neonatal care, surgical repair, and respiratory support requirements and outcomes were recorded and analyzed.

2.1. Prenatal MRI and Echographic Acquisition

Omphalocele diameter, omphalocele collar, and abdominal and cranial circumference were assessed from prenatal ultrasound studies. Pulmonary volumes were calculated from prenatal MRI (Ingenia, 3 Tesla in T2 sequence) using the Rypens et al. method [17]. Lung tissue was manually outlined in each slice of a single sequence, and volume was obtained by multiplying by slice thickness. Observed-to-Expected fetal lung volume was calculated by comparing that expected for gestational age from reference tables. The interpretation was made by radiologists who had experience with the technique to routinely assess lung volume in other diseases associated with pulmonary hypoplasia. Pulmonary hypoplasia was defined as an Observed-to-Expected pulmonary volume of less than 50%.

2.2. Surgical Care

The main goal of the treatment consisted of closing the abdominal wall without inducing a life-threatening increase in intra-abdominal pressure [18]. The paint-and-wait treatment was chosen by our surgical team because this technique has previously shown a faster hospital discharge, initiation of full enteral feeding, and decreased incidences of late-onset infection [6].

The paint-and-wait procedure consisted of suspending the herniated sac by the umbilical cord immediately after birth. In addition, we applied a dressing on the omphalocele until the cutaneous epithelium was covered. In our center, we used fatty dressing (Vaseline Cooper©). This treatment allowed the closure of the abdomen by obtaining a cicatricle skin covering the medial ventral hernia. Definitive abdomen closure is proposed for children between 1-year-old and 2-years-old, mainly after walking achievement.

2.3. Postnatal Management

Neonatal medical records were studied, and neonatal outcomes were analyzed: gestational age at delivery, birth weight, APGAR score, blood gases, type of resuscitation, duration of mechanical ventilation, age at first and last closure procedure, duration of total parenteral and enteral feeding, timing to the first hospital discharge and major complications. Delayed surgical closure was used in all patients.

Postnatal outcomes included the type of surgical repair, duration of ventilation and O2 supplementation, white blood cells (WBC) count, hemoglobin count, blood platelets count, C-reactive protein (CRP) concentrations, and gastroesophageal reflux disease with or without the need for surgery**.**

2.4. Late-Onset Infection

We defined a late-onset infection as clinical sepsis associated with an elevation of CRP > 5 mg/L and proven by a positive bacterial culture (blood, urine, and cerebrospinal fluid). Every increase in CRP level was associated with multiple bacterial samplings (blood and urine). A late-onset infection could be septicemia, pyelonephritis, an infection of the central line, or pulmonary infection.

2.5. Prolonged and Short Inflammatory Syndrome

Prolonged inflammation was defined as a CRP concentration above 20 mg/L for more than 15 days, a platelet count of more than 500 G/L for more than 15 days, and a WBC count of more than 15 G/L for more than 15 days, as opposed to the usual definition of acute inflammation which resolves in less than two weeks [19]. We defined brief inflammatory syndrome as a CRP level higher than 20 mg/L for less than ten days. We did not use average CRP because of the strong influence of extreme values, which made it difficult to interpret.

2.6. Primary Outcome

All patients underwent Doppler echocardiography by an experienced neonatologist or pediatric cardiologist in the first week after birth [20]. The following variables were measured in all patients: blood flow velocities in the left pulmonary artery and the ductus arteriosus (DA), pulmonary and/or tricuspid regurgitation gradient, and assessment of the shape of the interventricular septum. Pulmonary hypertension was defined as a combination of the following criteria:

- Right-to-left or bidirectional flow in DA;

- Flattening or paradoxical septum if DA is not present;
- Mean blood flow velocity less than 0.25 m/s in pulmonary arteries;
- Pulmonary or tricuspid regurgitation gradient above 50% of systemic systolic pressure if DA is not present;

  Inhaled NO and/or Sildenafil were used in the case of PH.

2.7. Statistical Analysis

Categorical variables are expressed in terms of frequencies and percentages. Quantitative variables are expressed as means ± standard deviation (SD) in the case of normal distribution or medians (interquartile range (IQR)). The normality of distributions was checked graphically and by using the Shapiro–Wilk test.

Patients with PH were compared to patients without PH using the Chi-square test (or Fisher's exact test in case of expected value < 5) for categorical variables and the Mann–Whitney U test for quantitative variables.

Statistical testing was conducted at the two-tailed α-level of 0.05. Data were analyzed using the SAS software version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Population

One hundred and twenty omphaloceles were assessed for eligibility between November 1996 and September 2021. As we can see in Figure 1, the final studied population included 50 patients with isolated giant omphaloceles. Antenatal and neonatal characteristics are described in Tables 1 and 2, respectively. Except for a slight difference in Apgar score at 1 min, there were no other significant differences in neonatal characteristics between the two groups.

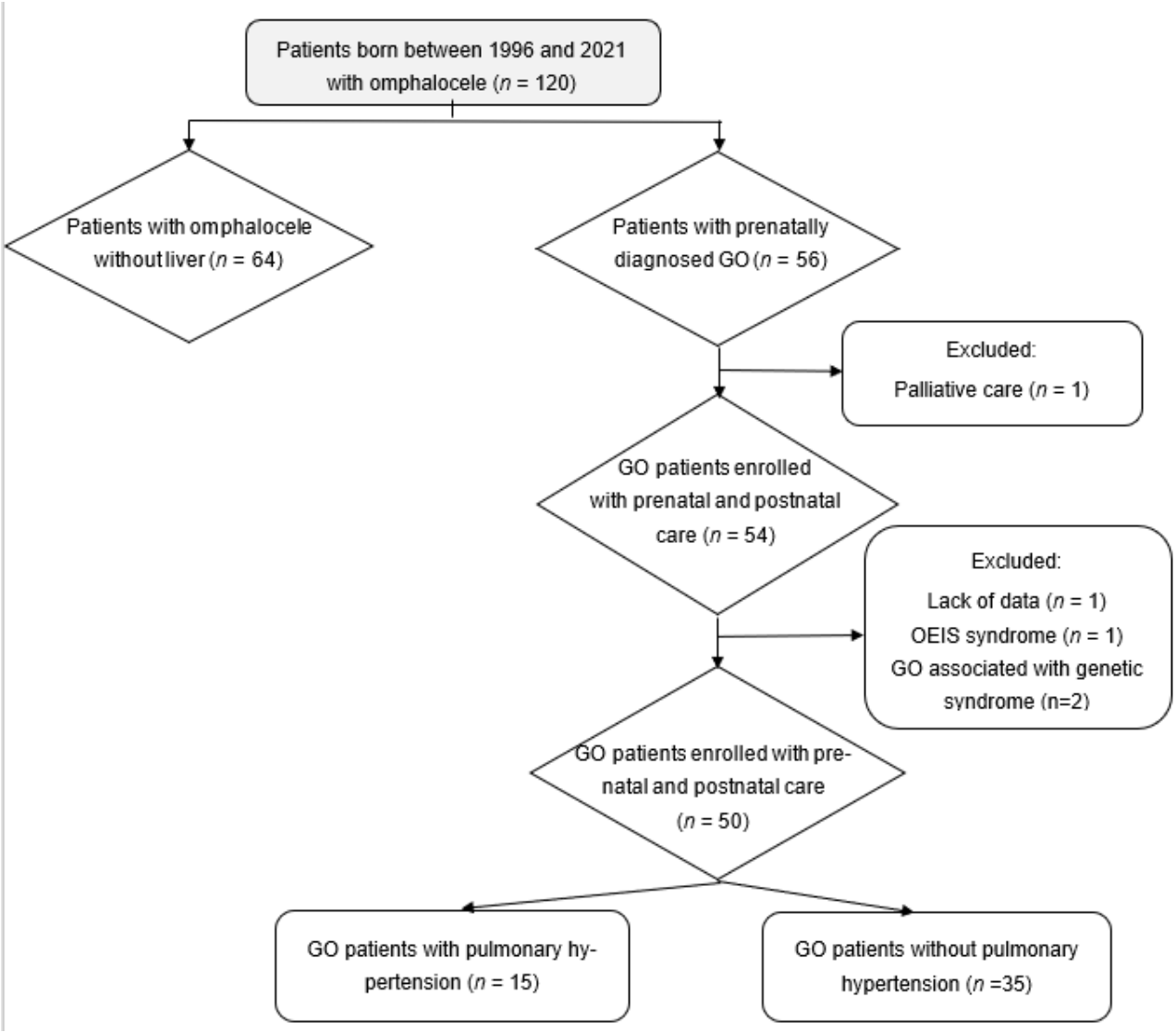

Figure 1. Flow chart of the study population. Abbreviation: GO, giant omphalocele, OEIS, omphalocele-cloacal exstrophy syndrome.

Table 1. Antenatal characteristics.

	GO with PH (n = 15)	**GO without PH (n = 35)**	***p*-Value**
Pulmonary hypoplasia (Rypens) (n = 28)	3/7 (43)	6/21 (27)	0.64
Ratio CO/CA at T2 (n = 10)	1.01 [0.97–1.05]	0.82 [0.74–0.93]	
Ratio CO/CA at T3 (n = 8)	0.95 [0.89–1.02]	0.72 [0.65–0.75]	
Ratio CO/CC at T2 (n = 10)	0.67 [0.66–0.80]	0.67 [0.58–0.71]	
Ratio CO/CC at T3 (n = 10)	0.64 [0.63–0.73]	0.64 [0.58–0.67]	
GO collar at T2 mm (n = 30)	25 [22–30]	24 [20–30]	0.76
GO collar at T3 mm (n = 24)	39 [37–45]	47 [29–52]	0.83
GO collar at MRI evaluation mm (n = 18)	38 [35–44]	40 [30–50]	0.93

Values are expressed as numbers/total numbers (percentage) or medians (interquartile range). Abbreviations: d, days; GO, giant omphalocele; CO, omphalocele circumference; CA, abdominal circumference; T2, second trimester; T3, Third trimester.

Table 2. Neonatal characteristics.

Variable	GO with PH (n = 15)	GO without PH (n = 35)	*p*-Value
Male, n (%)	5 (33)	17 (48)	0.5
Birth weight (g), mean ± SD	2586 ± 792	2838 ± 1000	0.44
GA at delivery (wks), mean ± SD	36 ± 3	37 ± 2	0.1
Apgar at 1 min, median [IQR]	9 [4–10]	10 [6–10]	<0.05
Apgar at 5 min, median [IQR]	10 [8–10]	10 [8–10]	0.2
Venous umbilical cord pH[1], mean ± SD	7.32 ± 0.04	7.33 ± 0.06	0.6

Values are expressed as numbers (percentage) unless otherwise stated abbreviation: GA, gestational; IQR: interquartile range; SD: standard deviation.

3.2. Fetal Echographic and MRI Assessment

The median omphalocele's collar circumference in the second and third trimesters of gestation was 25 [22–30] mm and 39 [37–45] mm, respectively. The median gestational age at fetal MRI evaluation was 32 weeks. The mean pulmonary volume was 37.9 +/− 9.7 mL. Among 26 giant omphalocele cases who underwent fetal MRI, 13 showed a pulmonary volume of less than fifty percent.

3.3. Outcomes

The mean duration of hospitalization was 62 days. Overall survival until discharge was 96%. Fifteen patients (30%) developed pulmonary arterial hypertension within the first month of hospitalization. Two children died because of PH at 132 and 180 days of age. Nitrogen monoxide was used in 24% of cases, and Sildenafil was used in 14%. Among GO neonates, 20% were intubated on the first day of life. The mean duration of invasive ventilation was five days. Three (6%) of the GO neonates required

tracheostomy placement. The mean duration of parenteral nutrition was 28 days. Ten patients (20%) needed gastrostomy tube placement. Furthermore, 54% of GO patients needed medication such as omeprazole for gastroesophageal reflux disease, and 10% underwent a Nissen fundoplication. All of our patients were treated with delayed surgical closure; the median age of surgical closure was 360 days of life.

There was no significant difference between the two populations of GO (except at 1 min Apgar), although a trend was identified toward infants with PH being smaller in weight and gestational age. As we can see in Table 1, patients with PH showed no difference in terms of pulmonary hypoplasia according to Rypens et al., with pulmonary hypoplasia occurring in 20% of patients in the PH group and 17% of patients in the no PH group ($p = 0.64$). There were no significant differences in other measures, such as the ratio of omphalocele circumference and abdominal circumference or the ratio of omphalocele circumference and cranial circumference. As we can see in Table 3, two deaths occurred in the PH group (13%), but none occurred in the group without PH. We observed an inflammatory state, defined as an increase in CRP level of more than 20 mg/L over more than 15 days during the first month of life, occurring in 73% of patients with PH versus 21% of patients without PH ($p < 0.05$). Furthermore, brief inflammation duration is not associated with PH. As shown in figure 2, there was no difference between the two groups with proven secondary infection, showing that this inflammatory state was not related to bacterial infection.

Variable	GO with PH (n = 15)	GO without PH (n = 35)	*p*-Value
DOL at final abdominal closure (d)	425 [13–790]	296 [1–1125]	0.51
Duration of parenteral feeding (d)	43 [5–381]	9 [0–40]	0.09
Enteral nutrition			
DOL at initial feedings (d)	5.5 [0–30]	1 [0–15]	0.16
DOL on full goal volume feedings (d)	43 [5–375]	13 [0–40]	<0.05
Need of gastrostomy tube, n (%)	7 (46)	3 (8)	<0.05
Length of supplemental O2 > 30% (d)	8 [0–60]	0 [0–5]	<0.05
Need for GERD medication, n (%)	13 (86)	15 (43)	<0.05
Need for tracheostomy, n (%)	2 (13)	1 (2.8)	0.2
Duration of mechanical ventilation (d)	15 [0–56]	0 [0–8]	<0.05
Mechanical ventilation > 14 d, n (%)	9 (60)	0 (0)	<0.05
Death, n (%)	2 (13)	0 (0)	<0.05

Table 3. Outcome

Values are expressed as numbers (percentage) or median [IQR]. Abbreviation: d, days; DOL, day of life; g, gram; wks., weeks; GO, giant omphaloceles; GERD, gastroesophageal reflux disease; IQR: interquartile range; SD: standard deviation.

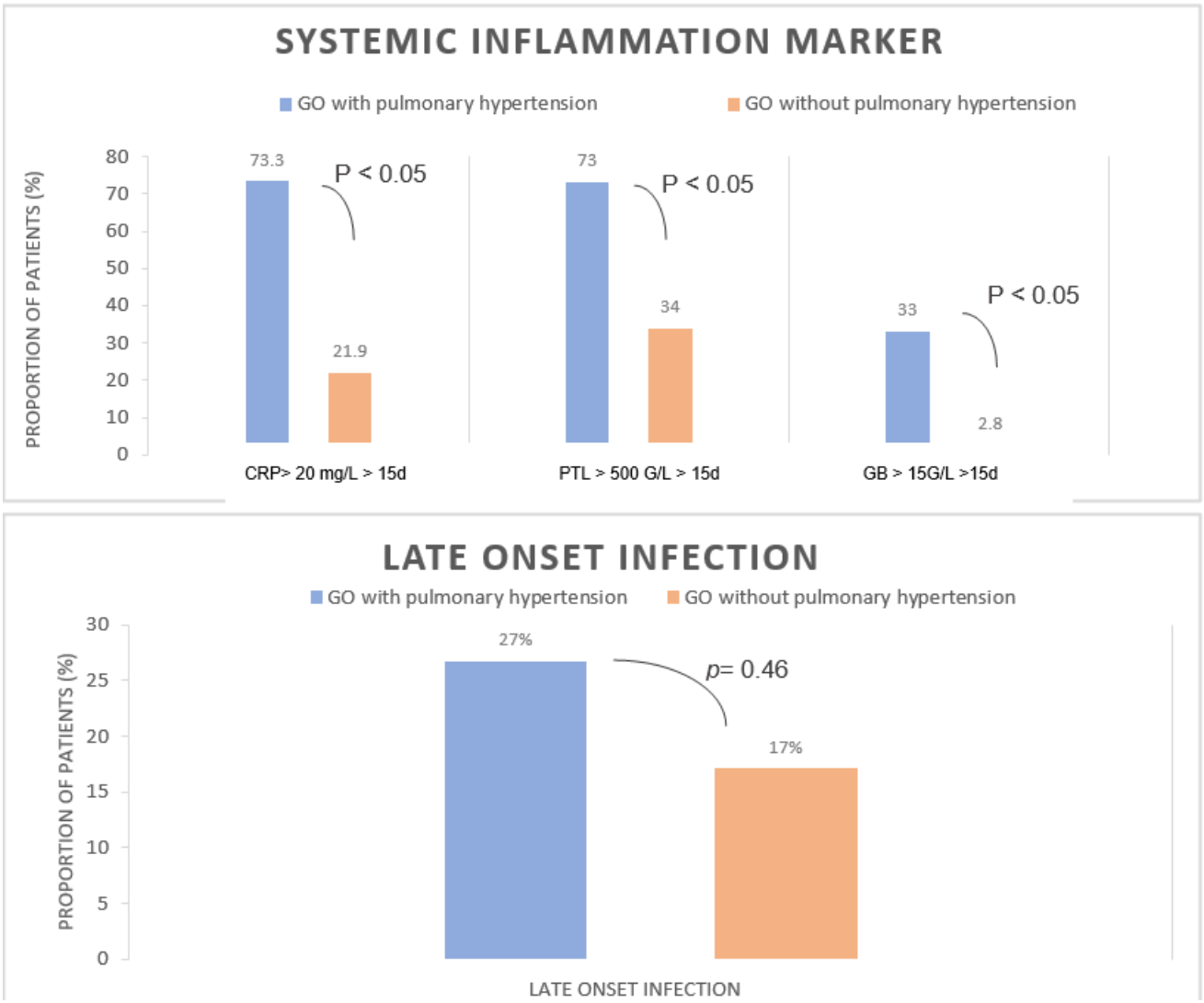

Figure 2. Comparison of systemic inflammation markers in GO with and without PH onset. Comparison of late-onset infection between GO with PH and GO without PH. Abbreviations**:** CRP, protein C-reactive; WBC, white blood cell; d, days; GO, giant omphalocele; PLT, platelet.

4. Discussion

The aim of this study is to determine the prenatal and neonatal factors associated with the development of PH in patients with isolated giant omphaloceles, considering that PH plays a key role in morbidity and mortality in this population. We designed a retrospective population-based study where all patients with giant omphaloceles who were born in our region were included from 1996 to 2021. Several limitations must be acknowledged. Because of its retrospective design, we cannot rule out that some patients may not have been included in the study. However, it is unlikely, as special care has been taken to ensure the completeness of the reports by matching different

databases. Although the rate of late-onset infection was not significantly different between the two groups, we cannot exclude that the difference may exist in a larger study, particularly due to the extension of the duration of invasive management in infants with PH. Furthermore, a single observer and a lack of MRI lung evaluation limited the interpretation of pulmonary hypoplasia.

However, this study is one of the largest to examine the prenatal and postnatal outcomes of giant omphaloceles. The survival rate is high (96%) in our study and consistent with the literature [4,8,16]. However, one-third of giant omphalocele cases in our population developed PH, and our results indicate that a prolonged inflammatory syndrome is associated with an increased risk of PH. GO newborns with PH have a lower survival rate and higher respiratory and digestive morbidities.

In general, the omphalocele sac can exhibit considerable heterogeneity regarding size or contained viscera, and additionally, the presence of other malformations or chromosomal abnormalities significantly influences the prognosis of the affected newborns. For instance, isolated small omphaloceles are known to have a favorable prognosis. Conversely, isolated GO is associated with more respiratory failure, delayed full enteral feeding, a higher need for GERD medication or Nissen surgery, and neurodevelopmental delay [20–22]. A high incidence of digestive morbidities was found in our cohort. Furthermore, Partridge et al. showed that 37 percent of GO patients developed PH, which is consistent with our data. PH is known to be associated with longer NICU length of stay, longer mechanical ventilation, and almost 15% mortality [20]. This is in alignment with our study, which showed a significant excess of mortality in the GO with PH group.

Vascular tonicity is frequently abnormal in pulmonary hypoplasia and induces a significant increase in mortality and poor long-term outcomes in patients with lung maldevelopment, such as congenital diaphragmatic hernia (CDH) [23,24]. In CDH, a rise in pulmonary vessel reactivity has also been associated with pulmonary hypoplasia, including decreased response to vasodilator stimuli [25]. However, Danzer et al. failed to show a link between lung volume and PH, probably because of the more complex pathophysiology in GO [16]. In our study, the prenatal markers of pulmonary hypoplasia or the size of the GO were not associated with PH. Although studies suggested that a narrow thorax and omphalocele on abdominal circumference ratio are associated with PH [26], they failed to understand the whole mechanism underlying PH-related GO. Indeed, PH tends to worsen in the first weeks after birth, suggesting

postnatal mechanisms. Our results indicate that some infants with giant omphalocele exhibit prolonged inflammatory syndrome that is mostly independent of infection. The data provide evidence that PH's development in GO is associated with sustained inflammation. To the best of our knowledge, the present study is the first to highlight that inflammation is part of PH development in GO.

However, it is described in the literature that the inflammation process is linked to altered vascular cell metabolism. Correlation of the average perivascular inflammation score with vascular thickness with respect to mean pulmonary arterial pressure has been reported [15]. The fact that inflammation precedes vascular remodeling in experimental PH suggests that altered immunity is a cause of vascular disease [14]. Biomolecular studies show that activated CD8+ T cells contribute to the pathogenesis of PH through TNF-alpha activation. Several changes through this mechanism result in proliferation within the pulmonary artery wall, a hallmark of pulmonary arterial hypertension [27]. IL-6 overexpression in a mouse model induced the development of PH through the induction of FGF2 and the activation of the transcription factor KLF5 [28]. In addition, it has been proved in both experimental and clinical studies that neutrophil elastase can influence pathogenesis [29]. Indeed, in the mouse model, elastase inhibitor elafin repressed the development and progression of PH [29–31].

At our center, patients with evidence of elevated pulmonary pressures were assessed by echocardiography approximately once a week. Taking into account the one-third rate of PH in giant omphalocele, screening for PH should be performed within the first week of life in all patients, with echocardiography performed at regular intervals. The association of inflammatory syndrome and PH associated with GO is described for the first time. Mechanisms are not fully delineated and could be multifactorial. We hypothesize that the inflammatory syndrome emerges from a primary lesion of the liver or is related to delayed abdominal closure and skin inflammation. Currently, we use a delayed closure of the abdominal defect that could be responsible for significant inflammation around the peritoneal sac linked to local and chronic infection between the skin and the peritoneal sac. Several studies have shown interest in treating inflammation associated with PH [32]. However, further studies are required to evaluate whether inflammation management may improve the prognosis and management of short- and long-term complications.

5. Conclusions

Our series highlights that pulmonary hypertension may worsen the outcome of giant omphalocele patients. We identified that prolonged inflammatory syndrome is associated with PH development. Further studies focusing on inflammation and altered immunity in giant omphalocele treated by delayed surgical closure may promote a new management strategy to prevent GO-related morbidity.

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Discussion

L'objectif de notre étude était de déterminer les facteurs prénataux et néonataux associés au développement d'une hypertension pulmonaire chez des patients atteints d'omphalocèles géantes, cette hypertension pulmonaire jouant un rôle central dans la morbidité et la mortalité dans cette population. Nous avons donc réalisé une étude rétrospective en population en incluant tous les porteurs d'omphalocèles géantes nés dans la région entre 1996 et 2021. Le taux de survie dans notre étude était élevé (96%) ce qui est cohérent avec les données issues de la littérature [23,27,28]. Cependant, un tiers des patients porteurs d'omphalocèles géantes développaient une HTP et nos résultats indiquent qu'un syndrome inflammatoire prolongé est associé au développement de cette HTP . Ces patients présentaient une survie moins importante et une augmentation des morbidités digestive et respiratoire.

Il peut exister une grande hétérogénéité concernant la taille et le contenu du sac de l'omphalocèle, et cette présentation variée, associée à la présence d'anomalies structurelles ou chromosomiques, influencent grandement l'évolution des nouveau-nés. Par exemple, les patients porteurs de petits omphalocèles isolés sont connus pour avoir un bon pronostic [29,30]. Au contraire, les patients porteurs d'omphalocèles géantes isolées présentent plus d'épisodes d'insuffisance respiratoire, un délai plus important à l'autonomie alimentaire, une incidence plus élevée de reflux gastro-œsophagien ainsi qu'un retard neurodéveloppemental.

Ces résultats de la littérature sont en accord avec notre étude où nous démontrons une augmentation significative de la morbi-mortalité chez les patients porteurs d'omphalocèles géantes développant une HTP.

Il est décrit qu'un développement vasculaire pulmonaire anormal est fréquemment impliqué dans l'hypoplasie pulmonaire et représente une limitation significative à la survie et au devenir à long terme chez les patients porteurs de pathologies telles que

la hernie diaphragmatique congénitale [31,32]. De multiples anomalies fonctionnelles de la réactivité pulmonaire ont été rapportées chez les patients atteints d'hypoplasie pulmonaire incluant une mauvaise réponse aux stimuli vasodilatateurs [33]. Cependant, dans une étude recherchant les facteurs pronostics chez les porteurs d'omphalocèle géants, Danzer et al, ont échoué à mettre en évidence un lien statistiquement significatif entre hypoplasie pulmonaire et hypertension pulmonaire, probablement en lien avec une physiopathologie plus complexe chez les patients porteurs d'omphalocèles géantes [27]. Dans notre étude, ni l'évaluation anténatale de l'hypoplasie pulmonaire ni celle de la taille de l'omphalocèle géante n'étaient associées avec la survenue d'HTP. En effet, l'hypertension pulmonaire tend à se majorer les premières semaines de vie suggérant un mécanisme postnatal. Nos résultats révèlent qu'un syndrome inflammatoire prolongé existe chez les patients porteurs d'omphalocèles géantes, indépendamment de tout syndrome infectieux. Ces données soutiennent le fait que le développement d'une HTP est lié, au moins en partie, à la présence de ce syndrome inflammatoire prolongé. A notre connaissance, cette étude est la première à mettre en évidence que l'inflammation est impliquée dans le développement d'une HTP chez les enfants porteurs d'omphalocèles géantes.

Il est bien décrit dans la littérature qu'un mécanisme inflammatoire est inextricablement lié aux altérations vasculaires de l'HTP. En effet il existe une corrélation entre une inflammation vasculaire et un épaississement de l'intima, de la media et de l'adventice avec une augmentation des pressions pulmonaires moyennes [34]. De plus sachant que l'inflammation précède le remodelage vasculaire dans les modèles animaux d'hypertension pulmonaire, cela suggère qu'elle constitue une cause plutôt qu'une conséquence de cette pathologie [35]. Des études biomoléculaires ont montré que des lymphocytes T CD8 contribuent à la physiopathologie de l' HTP, via l'activation du

TNF-alpha, induisant de nombreux changements résultant en une succession d'apoptose et de prolifération cellulaire [36]. L'hyper-expression d'IL-6 via l'induction de FGF2 et l'activation de KLF5, induisait une HTP dans un modèle murin d'HTP. De plus il a été prouvé dans des études expérimentales et cliniques que l'élastase des neutrophiles est impliquée dans la genèse d'une HTP. En effet l'administration d'un inhibiteur d'élastase dans un modèle murin réprimait le développement et la progression de l'HTP [37–40].

Dans notre série, les patients suspects de pressions pulmonaires élevées étaient évalués par échographie cardiaque environ une fois par semaine. Si on prend en compte que le tiers de nos patients développeront une hypertension pulmonaire de gravité variable, un dépistage de l' HTP devrait être réalisé la première semaine de vie puis à intervalle régulier. L'association d'un syndrome inflammatoire au développement d'une HTP dans la population des omphalocèles géantes est décrite ici pour la première fois. Les mécanismes ne sont pas totalement élucidés et sont probablement multifactoriaux. Nous faisons l'hypothèse que ce syndrome inflammatoire pourrait être lié à une lésion primaire hépatique, organe central dans l'initiation et la poursuite de l'inflammation, ou bien à une inflammation chronique du pourtour cutané du sac herniaire. En effet actuellement nous utilisons une technique de fermeture dite de « tannage » qui pourrait être à l'origine d'une inflammation entre la peau et le sac péritonéal.

De nombreuses études ont montré l'intérêt de traiter l'inflammation associée à l'HTP [41]. Cependant, des études supplémentaires seront nécessaires pour évaluer si la prise en charge de l'inflammation pourrait améliorer le pronostic et l'évolution des patients porteurs d'omphalocèle géantes.

Conclusion

Notre étude montre que l'omphalocèle géante est une pathologie rare dont les morbidités néonatales et postnatales sont fortement liées à l'apparition d'une HTP. Nous avons identifié un syndrome inflammatoire chronique associé au développement de cette HTP.

Cette étude est la première à identifier ce facteur et l'étude de l'inflammation et de l'immunité dans cette population pourrait amener une toute nouvelle stratégie de prévention et de traitement de cette pathologie.

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Titre de la thèse : Un syndrome inflammatoire systémique est associé à la survenue d'une hypertension pulmonaire dans une population d'enfant porteurs d'omphalocèles géantes

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Cadre de classement : *Néonatalogie*

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Mots-clés : hypertension artérielle pulmonaire, omphalocèle géant, hernie diaphragmatique congénitale, inflammation

Résumé :
Notre objectif est de déterminer les facteurs périnataux contribuant au développement de l'hypertension pulmonaire (HTP) chez les patients porteurs d'omphalocèles géantes isolées (GO). Tous les cas d'omphalocèles ayant subi des soins prénataux et postnataux à l'hôpital universitaire de Lille entre 1996 et 2021 ont été examinés. Nous avons inclus tous les nourrissons atteints de GO isolée comprenant au moins une partie du foie et traitées par fermeture chirurgicale retardée. Les données prénatales et postnatales ont été enregistrées et corrélées avec les morbidités postnatales. Nous avons comparé les résultats entre un groupe de nourrissons atteints de GO ayant développé une HTP et un groupe de nourrissons porteurs de GO indemne. 120 nourrissons atteints d'omphalocèle ont été admis au CHU de Lille entre 1996 et 2021. Cinquante GO isolés remplissaient les critères d'inclusion de notre étude. L'incidence de l'HTP était de 30 %. Nous avons mis en évidence un état inflammatoire prolongé, défini comme une CRP supérieure à 15 mg/L, des plaquettes supérieures à 500 G/L et des globules blancs supérieurs à 15 G/l pendant plus de 14 jours chez les patients ayant développé une HTP. Cet événement s'est produit chez 73 % des patients atteints d'HTP contre 21 % chez les patients sans HTP ($p < 0,05$). L'infection tardive n'était pas différente entre les deux groupes. Nous avons émis l'hypothèse que le syndrome inflammatoire prolongé favorise l'HTP chez les nourrissons atteints de GO traités avec fermeture chirurgicale retardée.

<u>Composition du Jury</u> :

Président : Professeur Laurent Storme

Assesseurs : Docteur Rony Sfeir, Docteur Sébastien Mur, Docteur Pascal Vaast

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