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Original article

Morbimortality of newborns with omphalocele in a Level III Neonatal Intensive Care Unit

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Abstract

Background: Omphalocele is a midline abdominal hernia that conditions important rates of mortality and morbidity. Infants born with omphalocele present an increased risk of having structural and chromosomal anomalies or syndromes. It is a defect that requires surgical treatment with multiple postoperative comorbidities.

Purpose: To identify and characterize the cases of omphalocele of a Level III Neonatal Intensive Care Unit and analyse the impact of clinical and demographic characteristics of both infant and mother in patients' outcome.

Methods: This is a retrospective study based on the record analysis of infants that have been hospitalized in the Neonatal Intensive Care Unit of "Centro Hospitalar de São João" with the diagnosis of omphalocele between 2003 and 2012. Sixteen patients fulfilled these criteria. For each one, data about pregnancy, maternal history, prenatal diagnosis, delivery, newborn, treatment and follow-up was collected and analysed.

Results: The mean birth weight was 2,761 grams and the mean gestational age was 37 weeks. Prenatal diagnosis was performed in 12 (75%) of the cases; mean gestational week of diagnosis was lower in patients that died. Overall, 50% (80% of deceased patients) had large defects. Major malformations were seen in 25% of cases most often in deceased infants. Low 1st minute Apgar score, need of inotropic support, more days of parenteral nutrition and lower birth weight had statistically significant impact on mortality. After surgical correction 31.3% died, 18.8% had a residual hernia and 12.5% a gastroesophageal reflux, respectively.

Conclusion: The mortality rates of patients with the diagnosis of omphalocele are not negligible because of associated anomalies or postoperative complications. We have been able to correlate some clinical features with mortality and found out that patients who survive can have other comorbidities mainly in the first years of life. However the majority of infants are expected to have a good long-term development and quality of life.

Keywords

Omphalocele, congenital abnormalities, abdominal wall defects, prenatal diagnosis, outcome, newborn.

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Introduction

Omphalocele is a midline abdominal hernia with an estimated incidence that ranges between 1.5 and 3 in 10,000 live births [1]. It is covered by a membrane consisting of 3 layers (peritoneum, amnion and Wharton's jelly) [1, 2]. The contents of the sac can include either abdominal and/or pelvic viscera yet bowel and liver are the most frequent organs involved and usually remain morphologically and functionally normal [3]. The diagnosis can be performed by a routine prenatal ultrasound after the 10th postmenstrual week [4].

This is a congenital malformation that can be associated with important rates of mortality as well as long and short-term morbidity. Infants born with omphalocele have an increased risk of having structural and chromosomal anomalies or syndromes as well as an increased incidence of intra-uterine growth restriction, fetal death and premature labour [1, 5]. It is a defect that requires surgical treatment which leads to multiple postoperative complications [6]. The size of the hernia is important to predict prognosis [7]. Patients can have several long-term medical problems such as gastroesophageal reflux, pulmonary insufficiency, recurrent lung infections and feeding disorders with failure to thrive [3].

The purpose of this study is to identify and characterize the cases of omphalocele of a Level III Neonatal Intensive Care Unit during a 10-year period and to analyse the impact of clinical and demographic characteristics of both infant and mother in patients' outcome.

Material and methods

We searched the databases of Neonatology Care Unit of "Centro Hospitalar de São João" to identify newborns who were admitted with the diagnosis of omphalocele from 1 January 2003 and 31 December 2012. There were 16 patients that fit these criteria.

Data were collected retrospectively by reviewing maternal and neonatal records. Maternal information collected included age, weight, weight gained during pregnancy, height, parity and history of previous or familiar congenital diseases. Pregnancy and prenatal data included the occurrence of fever, gestational diabetes or IUGR, alpha-fetoprotein maternal levels, drugs used during pregnancy, amniotic fluid volume, week and method of diagnosis, karyotype, mode and week of delivery. Neonatal information included gender, birth weight, Apgar scores, birth temperature, cardiac and respiratory frequencies, glycemic levels, blood pressure, pre and postoperative pH, characteristics of the omphalocele, associated structural anomalies or genetic syndromes, treatment, feeding features, total length of hospital stay, postoperative ventilatory and inotropic support and neonatal outcomes of interest. Mothers of live infants were contacted to confirm some data about pregnancy and follow-up of patients.

For the purpose of this study a major anomaly was defined as an anomaly or malformation that creates significant medical problems for the patient or require specific surgical or medical management. A large omphalocele was considered when the diameter was superior to 4.5 cm [8].

The Ethics Committee of our institution approved the retrospective study.

Data collection was performed using *Microsoft Excel v.14.0.0*® and the statistical analysis was performed using *IBM SPSS statistics 22*®. The categorical variables were characterized by absolute and relative frequencies and continuous variables by mean (± standard deviation) if they had symmetric distribution and by median (minimum-maximum) if they had asymmetric distribution. We used Fisher's exact test to analyse the categorical variables and Independent t test and Mann-Whitney U test for continuous variables, symmetric and asymmetric respectively. A p value inferior to 0.05 was considered statistically significant.

Results

Demographic characteristics of our patients are presented in **Tab. 1**; **Tab. 2** sums up maternal characteristics.

The median number of previous gestations was 2 (min-max: 1-4) and deliveries were 1 (min-max: 0-3) with 5 mothers having former abortions and 1 having 2 former ectopic pregnancies. Three mothers had gestational diabetes; 3 needed antibiotics during pregnancy, 5 and 10 undertook vitamins and folic acid, respectively. Alpha-fetoprotein maternal levels were elevated in 2.

Prenatal diagnosis was made in 12 (75%) cases (1 was performed by magnetic resonance and the remaining by ultrasonography) with 4 (25%) infants being diagnosed only at delivery (1 of them with prenatal diagnosis of gastroschisis). The median week of diagnosis was 19 (min-max: 12-37) being lower in deceased group (15 weeks vs 22 weeks), p = 0.141 (**Tab. 2**). The karyotype was normal in 15 cases and unknown in 1. The amniotic fluid was abnormal in 2 pregnancies and intrauterine growth restriction (IUGR) was found in 2 (12.5%) pregnancies, both of them in patients who lived (18.2%, p = 0.838) (**Tab. 2**). Multiple pregnancies (n = 2; 12.5%) were only seen in patients who ended up dying, p = 0.083.

There were 4 pregnancy terminations due to omphalocele during the course of the study, 2 of them due to omphalocele size, 1 to fetal concomitant complex heart pathology and the other to fetal holoprosencephaly. These cases were excluded.

Cesarean delivery was the most frequent type of delivery (11 cases, 68.8%, 5 of which needed resuscitation at birth). Five (31.3%) patients had vaginal delivery, 2 of which needed birth resuscitation; in the deceased group the cesarean section was performed in 4 (80%) cases, p = 0.622 (**Tab. 3**).

The clinical characteristics of the infants are presented in **Tab. 3**.

Omphalocele was considered small in 6 (37%) cases and large in 8 (50%) cases. In the neonatal death group the frequency of large omphaloceles was remarkably higher (80% vs 36.3%, p = 0.301). The contents of the defect were mainly bowel in 11 (68.7%) patients and liver in 5 (31.3%). Only 2

Table 1. Demographic characteristics of patients who died and lived, respectively.

	Total (n = 16)	Deceased (n = 5)	Alive (n = 11)	p value
Gender, n (%)				
Male	7 (43.7)	2 (40)	5 (45.5)	0.838*
Female	9 (56.3)	3 (60)	6 (54.5)	
Gestational age, weeks, mean (± SD)	36.8 (± 2.4)	34.8 (± 3.3)	37.6 (± 1)	0.125§
Birth weight, grams, mean (± SD)	2,761(± 834)	1,998 (± 579)	3,108 (± 698)	**0.008**§

*Fisher's exact test, §Independent t test.

Table 2. Maternal characteristics of patients who died and lived, respectively.

	Total (n = 16)	Deceased (n = 5)	Alive (n = 11)	p value
Age, mean (± SD)	29.0 (± 5.4)	30.8 (± 3)	28.2 (± 6)	0.383§
Body mass index, median (min-max)	30 (23.7-39.2)	31 (29.7-39.2)	28.2 (23.7-35.3)	0.315¥
Obesity, n (%)	6 (37.5)	3 (60)	3 (27.3)	0.545*
Multiple pregnancy, n (%)	2 (12.5)	2 (40)	0 (0)	0.083*
Prenatal diagnosis, n (%)	12 (75)	5 (100)	7 (64)	0.505*
Prenatal diagnosis, weeks, median (min-max)	19 (12-37)	15 (12-18)	22 (12-37)	0.141¥
Complications during pregnancy, n (%)				
Gestational diabetes	3 (18.8)	1 (20)	2 (18.2)	0.931*
IUGR	2 (12.5)	0 (0)	2 (18.2)	0.838*
Antibiotics therapy	3 (18.8)	2 (40)	1 (9.1)	0.108*

IUGR:Intrauterine growth restriction.
*Fisher's exact test, §Independent t test, ¥Mann-Whitney U test.

Table 3. Clinical characteristics of patients who died and lived, respectively.

	Total (n = 16)	Deceased (n = 5)	Alive (n = 11)	p value
Type of delivery, n (%)				
Vaginal	5 (31.3)	1 (20)	4 (36.4)	0.622*
Cesarean	11 (68.7)	4 (80)	7 (63.6)	
Apgar Score, n (%)				
1st minute				
< 7	6 (37.5)	4 (80)	2 (18.2)	**0.036***
≥ 7	10 (62.5)	1 (20)	9 (81.8)	
5th minute				
< 7	3 (18.7)	2 (40)	1 (9.1)	0.214*
≥ 7	13 (81.3)	3 (60)	10 (90.9)	
Resuscitation at birth, n (%)	7 (43.8)	4 (80)	3 (27.3)	0.106*
Umbilical cord pH, median (min-max)	7.23 (7.12-7.39)	7.18 (7.12-7.27)	7.29 (7.12-7.39)	0.343¥
Arterial postoperative pH, median (min-max)	7.33 (6.98-7.41)	7.12 (6.98-7.41)	7.33 (7.28-7.41)	0.438¥
Omphalocele volume, n (%)[a]				
Small	6 (37)	1 (20)	5 (45.4)	0.301*
Large	8 (50)	4 (80)	4 (36.3)	
Omphalocele contents, n (%)				
Bowel	11 (68.7)	2 (40)	9 (81.8)	0.077*
Liver	5 (31.3)	3 (60)	2 (18.2)	0.217*
Other organs	2 (12.5)	2 (40)	0 (0)	0.077*
Omphalocele type, n (%)[b]				
With intact sac	9 (56.2)	3 (60)	6 (54.5)	0.400*
With ruptured sac	1 (6.2)	1 (20)	0 (0)	
Other major malformations, n (%)	4 (25)	3 (60)	1 (9.1)	0.063*
Genetic syndromes, n (%)	4 (25)	2 (40)	2 (18.2)	0.547*
Gastroesophageal reflux, n (%)	2 (12.5)	1 (20)	1 (9.1)	0.591*
Residual hernia, n (%)	3 (18.8)	0 (0)	3 (30)	0.371*
Stent placement, n (%)	4 (25)	3 (60)	1 (9.1)	0.063*
Other surgeries during hospitalization, n (%)	4 (25)	3 (60)	1 (9.1)	0.063*
Mechanical ventilation, n (%)	10 (62.5)	5 (100)	5 (45.5)	0.093*
Total parenteral nutrition, n (%)	11 (68.8)	3 (60)	8 (72.7)	0.611*
Inotropic support, n (%)	4 (25)	4 (80)	0 (0)	**0.003***
Days of mechanical ventilation, median (min-max)	3 (2-317)	5 (2-317)	3 (2-3)	0.095¥
Days of total parenteral nutrition, median (min-max)	7 (3-119)	56 (8-119)	6 (3-9)	**0.024¥**
Days of hospitalization, median (min-max)	8 (2-317)	8 (2-317)	8 (2-14)	0.913¥

*Fisher's exact test, §Independent t test, ¥Mann-Whitney U test.
[a]Unknown = 2; [b]unknown = 6.

(12.5%) patients had other structures present in the hernia such as spleen and stomach (in 1 case) and omentum in another. There were no statistically significant differences in sac contents between the two groups. However there was a propensity for the liver presence in the dead group (60% vs 18.2%, p = 0.217) and the presence of other structures was only seen in patients who died (40%, n = 2, p = 0.077). Bowel was present in 9 surviving infants (81.8%) and 2 patients (40%) who died, p = 0.077. Nine (56.2%) infants presented an intact sac and 1 (6.2%) had ruptured sac (p = 0.400).

Newborn Apgar score at 1st minute was < 7 in 6 patients (37.5%) with significant impact in the outcome (p = 0.036). The median umbilical cord pH was 7.23 (7.12-7.39) and median arterial post-operative pH was 7.33 (6.98-7.41). When comparing the two groups the median umbilical cord pH was higher in survivors than in non-survivors (7.29 vs 7.18) and the median postoperative arterial pH was 7.33 vs 7.12, however none of them had impact on outcome (p = 0.343 and p = 0.438, respectively).

Other major malformations were seen in 4 patients, 2 of them with cardiac anomalies, 1 with diaphragmatic eventration and 1 with neurologic malformation. Genetic syndromes were present in 4 patients, 2 with Beckwith-Wiedemann Syndrome (BWS), 1 with Cantrell Penthalogy and 1 with Pierre-

Robin Sequence. Major malformations were more frequent in patients who died (60%, n = 3) than in those who lived (9.1%, n = 1), but these differences were not statistically significant (p = 0.063).

All patients were operated during the first 24 hours of life. One patient underwent surgery in another institution. Four patients needed a stent placement and the same number was submitted to other surgeries during hospitalization either because of the omphalocele or other associated pathologies (both variables were present in 60% of the dead group and 9.1% of alive group, p = 0.063).

During the hospitalization time 4 infants (25%) had hemodynamic instability needing inotropic support. All these patients died, p = 0.003 (**Tab. 3**). Metabolic and electrolytic disorders occurred in 6 (37.5%) and 4 (25%) patients, respectively. Ten (62.5%) patients needed mechanical ventilation (100% of the deceased group and 45.5% of surviving patients, p = 0.093) during a median time of 3 days (min-max: 2-317) (slightly higher in non-survivors – 5 vs 3 days – without statistical significance) (**Tab. 3**).

The median day to start enteric feeding was day 3 of life (2-15). Two infants (12.5%) were never fed enterally. Total enteral feeding was achieved at day 8 (median, min-max: 2-228). Eleven patients (68.8%) had total parenteral nutrition (TPN) for a median time of 7 days (min-max: 3-119) and this had a significant impact on outcome, p = 0.024 (**Tab. 3**). Two patients presented abdominal compartment syndrome.

The median hospitalization length of stay was 8 days (2-317) (**Tab. 3**).

Five patients (31.3%) died at median age of 8 (2-317) days of life, 2 of whom were submitted to necropsy examination. Infants who were autopsied died from multiple organ dysfunction syndromes, 1 of them because of abdominal compartment syndrome and the other because of functional and metabolic immaturity.

On long-term follow-up 3 patients (18.8%) had a residual hernia (umbilical hernia was present in 2 and supraumbilical hernia in 1) and 2 (12.5%) had gastroesophageal reflux. All these patients had their conditions treated within the first 3 years of life. Ten patients had follow-up consultations in our hospital. The 2 patients with BWS had several comorbidities that justified their medical needs.

Discussion

Omphalocele is a congenital anomaly associated with several risk factors such as advanced and very young maternal age, African American race, maternal obesity, no use of multivitamins during pregnancy, disturbed glycemic control, maternal history of febrile illness, in vitro fertilization, mutations in several genes and abnormal mothers' karyotype [9]. We weren't able to study all these factors but we could notice that 37.5% of mothers were obese, which impacted on outcome.

Unlike previous studies where a male predominance of this pathology was noted [9], in our series there was a slight predominance of female patients.

In our study a low birth weight was significantly correlated to prognosis. Infants who died were clearly underweight. Our data is in accordance to other authors that reported similar results [6].

Although omphalocele diagnosis is usually made by a routine ultrasonography after the 10th postmenstrual week [4], we had some patients who were only diagnosed at birth. Overall the infants who died were diagnosed earlier, which is also reported by Nicholas et al. [10]. We hypothesised that this may be explained by the fact that larger defects may have a worst outcome [7] and are more likely to be detected earlier in the ultrasonography. On the other hand, we also know that alpha-fetoprotein maternal levels are elevated in 90% of cases [11, 12]. We couldn't get enough data to conclude whether the levels of alpha-fetoprotein correlate to outcome because only 2 mothers were referred as having elevated levels.

According to Ledbetter [1] up to 1/3 of patients have associated chromosomal anomalies. However, in more recent studies these have been found in 54-57% of patients [2]. Unlike these literature data, in our study all patients from whom we could access karyotype information presented a normal one.

This congenital anomaly is also associated with an increased incidence of IUGR in 5 to 35% of cases [1]. Our results are in accordance with this data since we found that 2 (12.5%) had IUGR and both of them survived.

It is important to consider the impact of prenatal diagnosis in the decision of interrupting pregnancy. In one study [13] it was noticed that more than 50% of pregnancies with omphalocele were interrupted and in another one they found that 37% of pregnancies with omphalocele were interrupted, even when isolated [14]. In our study 4 pregnancies were interrupted, 2 because of associated anomalies and the other 2 because of omphalocele size.

The optimal time of delivery is at term. However this pathology is usually associated with preterm

labour in 5 to 60% of cases [1]. We found out that there were more preterm patients in the deceased group although without statistical significance.

It is known that there is no improvement in neonatal outcomes for infants with abdominal wall defects who had cesarean delivery [15]. However, in accordance to other studies [7] cesarean delivery was the most frequent type of delivery in both groups.

There was a significant correlation between Apgar score at the 1st minute and outcome, since infants who had a score under 7 were mostly the ones who died. We also found the same tendency in the 5th minute score (without statistical significance).

The risk of an associated structural or chromosomal abnormality in an infant with omphalocele ranges from 27% to 63% [5]. In our sample the frequency was lower with associated major malformations or genetic syndromes found in 25%. The frequency of major anomalies was much higher in the deceased group and even though, as others [16], we found no statistically significant results, it has been described that this is one of the most important risk factor for both mortality and morbidity [2]. The most frequently associated structural anomalies are cardiac (30% to 50% of cases) and gastrointestinal malformations [1], which is actually what happened in our study. Genetic syndromes usually associated with omphalocele are BWS, pentalogy of Cantrell and OEIS (omphalocele, bladder or cloacal exstrophy, imperforate anus and spinal anomalies) [1]. There were 2 neonates with BWS in our series of cases; this has a reported prevalence of 13 to 33% in infants with omphalocele and normal karyotypes and since the diagnosis can be made prenatally it is of extreme importance to take this syndrome into account when counselling [16].

Past reports showed that the size of the defect has an important impact in the prognosis mainly if there are no associated anomalies and karyotype alterations [7]. Since our patients had normal karyotypes this is an essential aspect to take into consideration. Despite the fact that 37% of our cases had a small omphalocele, in the non-survivors group 80% of patients had an omphalocele considered large (36.3% in the survivors group). So, we can hypothesise that there is an important role of the size of hernia in the prognosis. It is still in discussion the exact cut-off that should be used in omphaloceles and it is very important to proceed to studies that help to understand what should be considered big enough to actually have a significant impact on outcome. Another subject of discussion is whether the extracorporeal liver can be sufficient to define an omphalocele as giant. According to some authors the presence of the liver in the sac is a predictor of reserved prognosis, however there are others that believe in the exact opposite theory [17]. In our sample we verified that in fact the majority of patients who had liver in the sac died and 60% of patients who died had it. Besides, 81.8% of the patients who lived and only 40% of patients who died had only bowel in the sac and all patients who had other structures involved in the hernia (such as omentum, bass and stomach) died. This gives us the idea that there are important differences and impacts in the outcome according to organs present in the sac. Islam [7] believes that the outcomes of ruptured omphalocele are substantially poorer than non-ruptured ones. We cannot support these results with our data since we only had 1 infant with ruptured sac who died.

The time and type of surgery vary according to the gestational age, size, characteristics of the defect, clinical status of the patient and the associated problems. For small omphaloceles the primary closure of the hernia should be done, however in larger defects this might be difficult due to the small abdominal cavity and the increased risk of intra-abdominal pressure. In this case a staged closure can be performed [3, 6]. What we actually verified in our study is that only 1 patient had 2 surgeries to repair the defect (all others had a primary closure and all patients had it in the 1st day of life). Sometimes it is necessary to place a prosthetic patch, preferably using a bio absorbable material to prevent infection [3, 6]. In our sample 25% of patients needed a prosthetic path and a correlation, although not significant, between its use and outcome was noted. Because there were no differences between the two groups concerning the type and time of surgery we can't conclude about the impact of it on the outcome.

Previous studies reported surgical morbidities in up to 27% of patients [16]. There are remarkable differences in the prognosis of patients with comorbidities when compared with the ones without them. Mechanical ventilation was seen in all patients who died and only in half the patients who lived who were ventilated for fewer days. Some authors reported that early respiratory distress or insufficiency were a strong predictor of poor outcome in large omphaloceles. Pulmonary complications are a significant survival limiting factor, namely pulmonary hypoplasia that is more

associated with large defects [7]. In our sample 25% of patients had pulmonary disorders. We also realized that the need of inotropic support because of hemodynamic instability is correlated with bad outcome, since all our patients that needed it ended up dying.

Because of the nature of the disease, most patients needed TPN. This is confirmed by our data that show TPN need in 68.8% of newborns. Even though it was more prevalent in survivors, actually the days of TPN were statistically correlated with the bad outcome.

Past reports have shown a perinatal mortality rate of approximately 30% [17] which was confirmed by our data, with isolated omphaloceles presenting survival rates between 75 to 95% [16]. Yet, as stated above, not only mortality but also morbidity are important. Besides the hospitalization and postoperative morbidity already discussed, when it comes to early life follow-up these patients usually undergo several surgeries both related to omphalocele and other pathologies. In our sample 25% of patients needed other surgeries during hospitalization. Some of them were because of residual hernias (35% of cases). According to Floortje et al. [18] gastrointestinal disorders are common in patients with omphalocele; our data support these findings since we have 12.5% of patients with gastroesophageal reflux, 1 infant with gallbladder stones and several cases of feeding problems and intolerance both during hospitalization and after discharge. However, all the patients were discharged from the consultation within the first 3 years of life except the 2 diagnosed with BWS that still needed medical support with several comorbidities not related directly with omphalocele. This makes us believe that if there are no associated anomalies the long-term quality of life is overall good, as stated by Floortje et al. [18], despite the several early life comorbidities and procedures these patients need.

Conclusion

Our data supports that the mortality rates of patients with the diagnosis of omphalocele are not negligible mainly because there are important comorbidities either related to the associated anomalies or to the postoperative complications. We have been able to correlate some clinical features such as the low Apgar score and the need of inotropic support as well as the time of TPN with mortality and found out that even patients who survive can have other comorbidities mainly in the first years of life. This should be considered when managing patients in early life, promoting predicting and preventing actions in order to increase the survival rates and the patients' quality of life. Even patients who have normal karyotypes and without associated anomalies can have poor outcomes but most frequently they are expected to have a good long-term development and a good quality of life.

Declaration of interest

The Authors declare that there is no conflict of interest.

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