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PRENATAL DIAGNOSIS AND SURGICAL INNOVATIONS IN CONGENITAL DIAPHRAGMATIC HERNIA: EVALUATION OF PRE- AND POST-OPERATIVE MANAGEMENT

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Abstract. Introduction. Congenital diaphragmatic hernia (CDH) is still today considered a challenge from surgeons. Considerable progress in prenatal diagnosis, intensive care unit of neonates and surgical techniques, with the possibility to perform minimally access surgery, widely increased survival rates. The aim of this study is to analyze our series about long and short-term outcomes, also considering the progress made by minimally invasive techniques. **Methods.** The study was performed at Pediatric Surgery of Siena. It is a retrospective study that analyzed all patients with CDH (Bochdalek) treated in the last 14 years, from 2000 to 2013. Sex, side of the defect, presence of prenatal diagnosis, age of onset and symptoms, associate malformation, herniated organs, surgical technique and site of surgery, complications, recurrences, survival and follow-up were analyzed. **Results.** We included 23 patients. Five of them, were ruled out because of affected by diaphragmatic eventration or acquired diaphragmatic hernia. Forteen patients (77%) presented left CDH and 4 patients (23%) a right one. The male female ratio were 14:4. Prenatal diagnosis was performed in 5 patients (27,5%) at a mean gestational age of 29 weeks. Forteen patients (77%) had an early onset of symptoms (first day of life). Most common symptoms were respiratory distress and cyanosis; 4 patients (23%) had a late onset of symptoms, at a mean age of 9 months, and most common symptoms were failure to thrive and vomiting. Seven patients (39%) had associated malformation: common mesenterium (5 pts-71%). The colon was the most commonly herniated organ, present in 15 patients (83%), followed by small intestine in 13 patients (72%), stomach in 11 patients (61%), spleen in 9 patients (50%) and liver in 4 patients (23%). Seventeen patients (94,5%) underwent open surgery: 10 of them (59%) underwent a subcostal laparotomy approach, 7 of them (41%) underwent a supra-umbelical laparotomy approach; 1 patient (5%) underwent minimally access surgery with thoracoscopy access. We performed performed surgery in the intensive care unit in 3 patients (16,5%). Six patients (33%) developed minor postoperatory complications. No patient had recurrence. Four patients died so we report a mortality rate of 23%. A follow-up investigation, with an average duration of 87 months, it is still going on in 5 patients (27,5%). **Conclusions.** The our survival rate was 77% and it reflects the encouraging reported data in the recent literature. These results are due to the reliability of the new resuscitation strategies, such as high-frequency oscillatory ventilation and the use of NO, the ability to perform surgery in the neonatal intensive care unit and, especially, to successfully perform minimally invasive surgery in newborn. The improvement of the survival showed the increasing of long-term morbidity end the requirement of a multidisciplinary follow-up. For these reasons, a multidisciplinary pathway for the management of young patients has been created, to follow them in a standardized way as early as the prenatal diagnosis.

Key words: Congenital diaphragmatic hernia (CDH), child, Minimally invasive surgery.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is one of the most common major congenital anomalies, with an incidence of 1 in 3000 live births worldwide [1].

Over the last years, improvement in prenatal diagnosis and new therapeutic approaches, as high-frequency oscillatory ventilation, inhaled nitric oxide, permissive hypercapnia, have been used for the management of these new-borns [2].

Today, surgery is therefore considered the least controversial part of the treatment of CDH. Minimally invasive surgery (MIS) for infants and children continues to grow and appears to be gaining added acceptance for CDH repair [3].

Average survival for CDH has improved from 50% to 70-80% and even up to 90% in some institutions [1].

We evaluate the influence of the progress of prenatal diagnosis, of the management in the neonatal intensive care unit (NICU) and of MIS CDH repair on patient's short- and long-term outcomes.

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MATERIALS AND METHODS

This is a retrospective study that was carried out in the Clinic of Paediatric Surgery of Siena (Italy). We identified patients from a prospectively kept database. We included all patients with CDH (Bockdalek) who were treated at our Institution between January 2000 and December 2013. Five patients were excluded because of affected by diaphragm event ratio or acquired diaphragmatic hernia. We analysed these patient's characteristics: demographics data, prenatal diagnosis (ultrasound foetal MRI and VR-Render), gestational age, delivery and birth weight, side of the defect, associated anomalies, symptoms and age of onset, postnatal management, surgical aspects (timing, location, technique and operative approach, herniated organs, using of a patch) short- and long-term outcomes. For the purpose of this study we defined emergency surgery when it was performed without reaching hemodynamic stabilization and deferred emergency surgery when it was performed after achievement of hemodynamic stability.

Statistical analysis were conducted to evaluate the correlation between prenatal diagnosis/method of delivery and type of ventilation strategy/surgery timing, and also to evaluate the possible association between complications and demographic data, associated malformations, side of CDH, ventilation strategies, surgical location and timing of surgical repair.

We statistically analysed the correlation between mortality and demographic data, associated malformations, side of CDH, herniated organs, ventilation strategy, timing of surgical repair and surgical location.

We used Fisher exact test and we considered statistical significance as $P<0.05$.

RESULTS

Eighteen patients were included: 14 (78.5%) male and 4 (21.5%) females.

Five patients (27.5%) presented at our observation with a prenatal diagnosis of CDH: in 4 cases (80%), it was performed only by ultrasound detection and 1 patient (20%) required foetal MRI to confirm the diagnosis. In this case we took advantage of a three-dimensional reconstruction technique called VR-Render. Prenatal diagnosis was performed at a mean gestational age of 29 weeks (range: 18-37 weeks).

Four patients (22%) were born preterm (32-36 weeks) with Low Birth Weight (LBW, range: 1890-2100 g). Ten patients (55.5%) carried out a caesarean delivery. Fourteen patients (78%) had a left sided CDH, 4 (22%) had a right sided defect. Nine (50%) babies showed associated anomalies (Figure 1).

Fourteen patients (78%) had an early onset of symptoms: all of them had respiratory distress and cyanosis, 3 patients (21.5%) showed additionally interstitial emphysema, hypotonia, haematological disorders.

The statistical analysis showed a significant association between the presence of a prenatal diagnosis and mode of delivery with a P-value of 0.035 (Table 1).

Four patients (22%) had a late onset of symptoms with vomiting, crying spells and growth retardation at a mean age of detection of 9.5 months (3 -16 months).

Table 1. Correlation between prenatal diagnosis and method of delivery.

P=0.035	Spontaneous	Cesarean	Total
Prenatal diagnosis +	0	5	5
Prenatal diagnosis -	8	5	13
Total	8	10	18

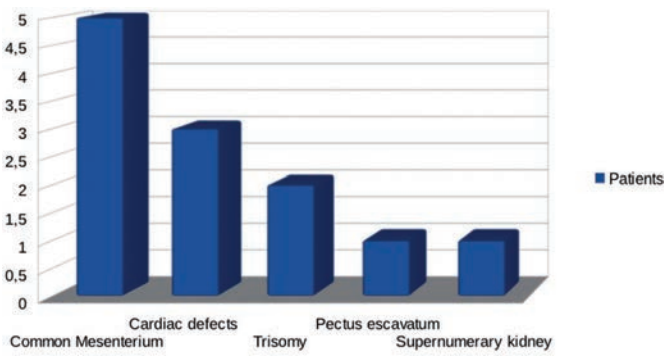

Figure 1. Associated malformation distribution in our series.

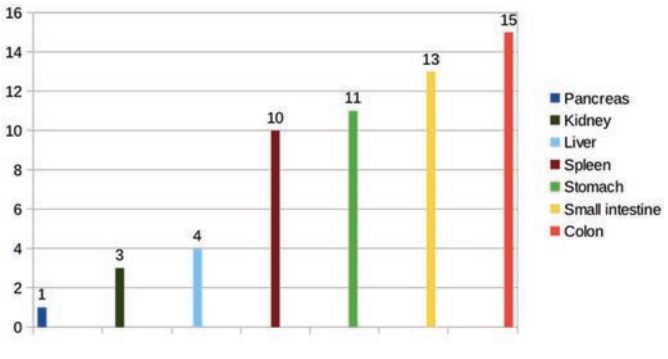

Figure 2. Herniated organs distribution in our series.

All patients (100%) underwent a preoperative chest-abdomen x-ray.

A gastric tube was placed in all patients and they were intubated.

Nine patients (50%) were ventilated with conventional strategy, (VCM) and 9 (50%) patients underwent High Frequency Oscillatory Ventilation (HFOV).

Six (33%) babies underwent surgery in emergency mode. Twelve (67%) babies underwent surgery in deferred emergency mode.

The correlation between ventilation strategy and surgery timing did not show a statistically significant difference, with a P-value of 0.62.

Fifteen patients (83.5%) underwent surgery in the operating room, 3 patients (26.5%) in NICU.

Seventeen (94.5%) patients underwent open surgery, 10 (59%) of them by a subcostal approach, 6 (35%) by sovraombellicale transverse approach, and 1 patient (6%) with a right thoracic approach. One patient (5.5%), underwent MIS with a thoracic approach.

Herniated organs are showed in Figure 2.

All patients underwent primary closure. No patch was placed.

Six patients (33%) developed postoperative complications: 4 of them (67%) developed bowel adhesions, 2 (33%) pneumothorax, 1 (17%) bilateral renal failure and 1 patient (17%) pneumonia associated with atelectasis. All complications were resolved, except for the patient with severe bilateral renal failure who died in the following days.

The statistical analysis showed that there was no statistically association between complications and demographic data, associated malformations, side of CDH, ventilatory strategies, timing of surgery and surgical location.

There were no recurrence in our series.

Death occurred in 4 patients (22%), respectively, for a marked pre-existing pulmonary hypertension, for severe malformations, due to the onset of a serious Multi Organ Failure (MOF) and severe acidosis followed by cardiac arrest.

The statistical analysis has shown that patients with low birth weight and premature infants are statistically associated with a worse prognosis in term of mortality with a P-value of 0.003 (Table 2). There was no correlation between mortality and associate malformations, side of the defect and herniation of stomach and liver. However our patient with trisomy showed higher mortality (P-value 0.08), such as patients who underwent HFOV and surgery in emergency mode (Tables 3-5).

There was no differences in mortality, instead, between patients underwent surgery in NICU and those underwent surgery in operating room (P=1.0).

Five patients (28%) were included in a follow-up program. The mean follow-up to date is of 87 months (62-112). All of them have regular values of weight and height during percentile, and a normal result of control x-ray. One patient (20%) repeated echocardiography and follow-up cardiology at 3 months due to associated cardiac malformations with normal results. One patient (20%) underwent an upper digestive system x-ray, due to a gastric volvulus with normal results.

DISCUSSION

The knowledge about the CDH are still evolving. Prenatal diagnosis has brought a great help, allowing to plan a caesarean birth in a tertiary centre, to perform surgery in the uterus in cases of severe pulmonary

Table 2. Correlation between mortality and weigh and gestational age at birth.

P=0.003	Deceased	Survivors	Total
LBW + preterm	4	0	4
ABW + term	0	14	14
Total	4	14	18

Table 3. Correlation between mortality an trisomy.

P=0.08	Deceased	Survivors	Total
Trisomy +	2	0	2
Trisomy -	1	6	7
Total	3	6	9

Table 4. Correlation between ventilation strategy and mortality.

P=0.08	Deceased	Survivors	Total
VCM	0	9	9
HFO	4	5	9
Total	4	14	18

Table 5. Correlation between mortality and timing of surgery.

P=0.08	Deceased	Survivors	Total
Emergency	3	3	6
Deferred emergency	1	11	12
Total	4	14	18

hypoplasia, or to terminate the pregnancy [4]. With its improvement the diagnosis can and should be made automatically in almost all cases [5]. It is interesting to note that in our series, 4 (80%) of the 5 cases with prenatal diagnosis are dated in the period between 2010 and 2013. In the light of these considerations, 4 of 7 patients, from 2010 to 2013, corresponding to 58%, have a prenatal diagnosis, highlighting an improvement, over time, of ultrasound detection. Similar to Literature, our study underlined the main role of prenatal ultrasound in providing a definitive diagnosis. We also confirmed that foetal MRI may help in case of difficult diagnosis, and we also benefit from a three-dimensional reconstruction technique as VR-Render (Figure 3). It is an interactive system for volume visualization which enables practitioners to quickly explore and analyse 3D medical or scientific data on a standard PC.

Optimizing ventilation strategy in patients with CDH may help to prevent chronic respiratory diseases. However evidence-based standardized treatment protocols are leaking in the field of this pathology. Consequently, ventilation strategies may differ between centres and ventilatory support is often based upon expert opinion [6]. To date, conventional ventilation is the most widely used , while in many institutions HFOV is used as rescue therapy. In some centres however, HFOV is used as the initial ventilation mode [7]. From our results HFOV seems to be associated with a higher mortality; however patients undergoing HFOV were the most uncompromising and probably this has affected the outcome of the statistical analysis. We think that this strategy may improve gas exchange, reduce barotrauma and decrease the presence of inflammatory mediators, reason why it has been used with a higher frequency in the last years.

Early CDH repair was thought to improve ventilation by reducing intrathoracic pressure after reduction of herniated viscera. However this strategy led to emergent procedures often performed on unstable infants. Reports started appearing in the mid-1980s suggesting that survival may be improved if surgery was delayed until preoperative stabilization was achieved, recognizing the impact of persistent pulmonary hypertension on survival [8]. In our opinion and due to our results, according to CDH EURO Consortium [9], even though there are no scientific evidence in favour of delayed surgery, we prefer reaching a preoperative hemodynamic stabilization.

Perform surgery in NICU carries on potential disadvantages including the risk of infection, inadequate lighting and delayed discharge. Lago *et al*. have argued, to now, the only study that analyses the outcome of the patients in the operating room than those operated in NICU [10]. They demonstrated that patients in the ICU have been shown to have a prevalence of: positive blood cultures (11 *vs* 0%), bronchial aspirate positive (16 *vs* 0%), postoperative mortality (33 *vs* 7%) and a longer hospital stay (26 *vs* 13%) [10].

However our results are comforting: there are no significant differences between the patients operated on in the operating room and in NICU in terms of postoperative complications and mortality: this leads us to think that the intervention in the NICU can be a viable alternative in all critically ill patients, in which transport to operating room may worsen their condition.

The proliferation of minimally invasive surgery (MIS) in paediatric surgery has allowed for the laparoscopic and thoracoscopic repairs of neonatal CDH to become routine in some institutions. The use of MIS approaches have been suggested to be advantageous over traditional open surgery, including less pain and incisional complications, avoidance of thoracotomy-related sequelae, as well as reduction of surgical stress [11]. Despite the wide-spread application of MIS, comparative outcomes remain elusive. Current evidence has been limited to case

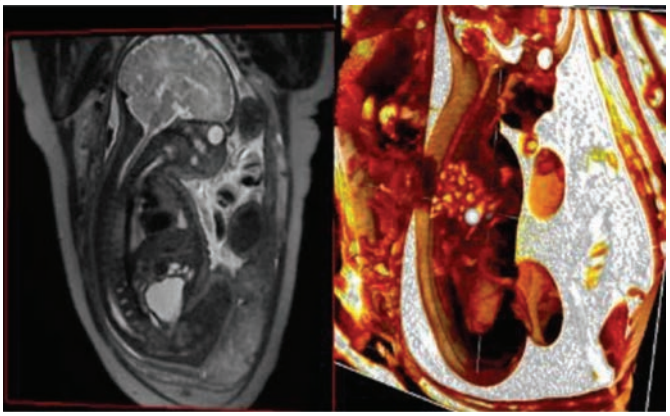

Figure 3. Fetal MRI and its 3-dimensional reconstruction by VR-Render.

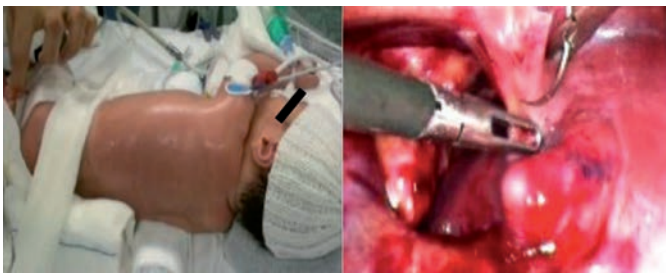

Figure 4. Positioning of the patient in the operating room and intraoperative corresponding image.

series and meta-analysis [12]. Our case had excellent results: the baby was discharged in day 9 postoperative and shows no recurrence, no complications neither long terms sequelae (Figure 4). It demonstrate that all cases with no compromises ventilatory parameters, pulmonary hypertension easily controlled with good prognosis can be successfully treated with minimally invasive techniques.

Several centres have shown that survival of patients with CDH is directly correlate with severity of pulmonary hypertension. Many studies have demonstrated that persistent sustained severe pulmonary hypertension is associated with significant worse survival [1]. Actually our study demonstrated the same results: our mortality is strictly correlated with premature and LBW infants who did never reach preoperative stabilization and underwent surgery in emergency mode. However our series reached 78% of survival, which is a very satisfactory result.

CONCLUSIONS

The interdisciplinary counselling between paediatric surgeon and neonatologist is crucial for the survival of the child: the CDH is a resuscitation emergency not surgical, therefore, the stabilization of the patients remain a key element.

Surgery is almost everywhere deferred to allow a better ventilatory and hemodynamic balance.

In addition our study underline that NICU, as a surgery location, can be a valid alternative to operatory room, showing no significant differences either in terms of postoperative complications, either in terms of mortality. In conclusion a multidisciplinary long-term follow-up is needed for this patients as it is showed from our study.

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