CASE REPORT

Bilateral Diaphragmatic Defect and Associated Multiple Anomalies

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Although congenital diaphragmatic hernia is one of the most common congenital anomalies, complete bilateral agenesis of the diaphragm is a very rare congenital malformation and frequently associated with other major anomalies. We report a case of bilateral diaphragmatic agenesis associated with major congenital anomalies. A 2,240-g male infant was born at 35 weeks of gestation to a 34-year-old mother with a history of minimal prenatal care. Polyhydramnios was reported on prenatal level 1 scan. The patient experienced early respiratory distress requiring intubation. Apgar scores were 2/1/1 at 1, 5 and 20 minutes, respectively, and efforts to resuscitate him were unsuccessful. He died at 2 hours of age. Autopsy revealed bilateral diaphragmatic agenesis associated with right pulmonary hypoplasia, left pulmonary agenesis, multiple cardiac abnormalities and gallbladder agenesis. Cytogenetic studies showed normal male karyotype. Bilateral agenesis of the diaphragm is a life-threatening malformation. Survival of these infants often depends on cardiopulmonary function. Bilateral agenesis of the diaphragm associated with gallbladder and unilateral pulmonary agenesis is a rare entity, and its clinical significance needs further investigation. [*J Chin Med Assoc* 2009;72(3):163–165]

Key Words: associated anomalies, bilateral diaphragmatic agenesis, gallbladder agenesis, pulmonary hypoplasia

Introduction

The development of the diaphragm occurs early in gestation via a fusion of the embryonic pleuroperitoneal membrane and the transverse septum. In the 3rd week of gestation, the fusion of the transverse septum with the dorsal mesentery of the foregut creates 2 openings whereby the thoracic and abdominal contents meet. In the 9th week of gestation, these openings close. Thus, any process that inhibits the closure of these channels may lead to defects in the diaphragm, including congenital diaphragmatic hernia (CDH) and diaphragmatic agenesis.[1]

Among the causes of severe respiratory failure in the newborn, congenital diaphragmatic defects remain the most life-threatening. Despite recent advances in prenatal diagnosis, neonatal intensive care and surgery, congenital diaphragmatic defects continue to have high mortality rates of up to 38–62%.[1,2] Although CDH is one of the most common congenital anomalies, complete bilateral agenesis of the diaphragm is a very rare variant.[3] Survival of infants with bilateral agenesis of the diaphragm often depends on cardiopulmonary function and whether or not other major congenital anomalies and chromosomal defects are present.[4–6]

Here, we present a case of bilateral diaphragmatic agenesis associated with major congenital anomalies. Autopsy findings are presented and related literature reviewed.

Case Report

A 2,240-g male baby was born at 35 weeks of gestation to a 34-year-old, gravida 1, para 0, woman by emergency cesarean section because of fetal distress. The mother had minimal perinatal care and no midtrimester anomaly screen. The emergency prenatal ultrasound that was performed before cesarean section demonstrated polyhydramnios. Family history was negative for consanguinity and genetic disorders. Weight, height and head circumference were within normal

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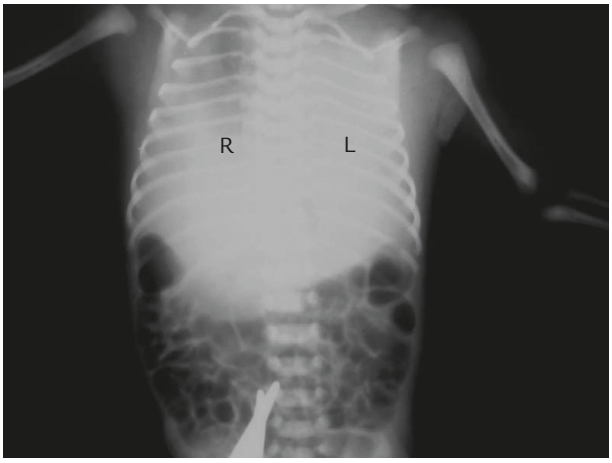

Figure 1. Chest X-ray shows minimal air in the right lung.

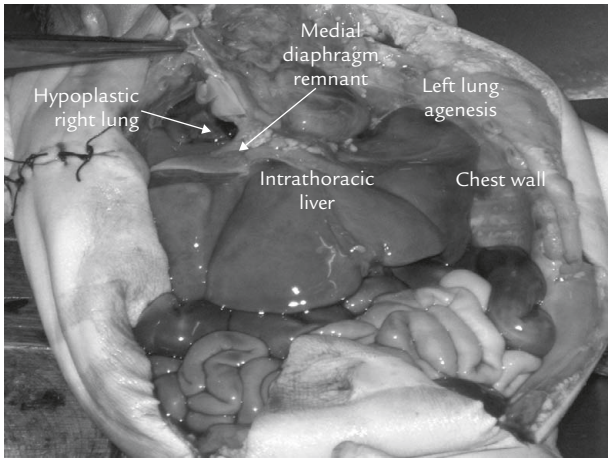

Figure 2. Autopsy reveals bilateral diaphragmatic agenesis and hepatic herniation.

percentiles for age. Apgar scores were 2/1/1 at 1, 5 and 20 minutes, respectively. The baby experienced early respiratory distress, was intubated in the delivery room, and transferred to the neonatal intensive care unit. He was placed on a pressure-limited, time-cycled ventilator set at peak inspiratory pressure (PIP) of 30 cmH_2O, positive end-expiratory pressure (PEEP) of 5 cmH_2O, a rate of 50 breaths/min, fraction of inspired oxygen (FiO_2) of 1.0, inspiratory time of 0.35 seconds, and flow of 8 L/min. The following arterial blood gas values were obtained from analysis of a sample from the umbilical artery catheter: pH 6.77, $paCO_2$ 102.9 torr, paO_2 34.4 torr, base excess –22.2, bicarbonate 12 mmol/L, and saturation 65%. Dopamine infusion was started because of hypotension.

Physical examination showed cyanosis, bradycardia and absent bilateral breath sounds. Chest X-ray demonstrated minimal air in the right lung, absent air and a large opacity in the left lung field (Figure 1). Despite aggressive resuscitative efforts, the patient died at 2 hours of age. During postmortem diagnostic right thoracotomy, liver and hypoplasic right lung were seen in the right side of the chest cavity.

Autopsy revealed bilateral diaphragmatic agenesis associated with right pulmonary hypoplasia, left pulmonary agenesis, left atrial and ventricular hypoplasia, large atrial septal defect, aortic over-ride of the septum, pulmonary artery aplasia and gallbladder agenesis with normal bile ducts. A major portion of the liver herniated into the thoracic cavity was identified (Figure 2). The large opacity in the left lung field on chest X-ray was due to the herniated liver. The pancreas and other organs were normal. Cytogenetic studies showed a normal 46,XY male karyotype. Genetic counseling and detailed ultrasonographic examinations during subsequent pregnancies were offered to the mother.

Discussion

CDH occurs in approximately 1 in 2,450 live births. Bilateral CDH, previously identified through a limited number of case reports, is extremely rare and has been reported to occur in just under 1% of neonates with CDH. Bilateral CDH is associated with a much higher incidence of associated anomalies and a higher mortality rate (65% and 33%, respectively) when compared with unilateral CDH.[7]

Although not many statistical studies exist in the literature on the survival of patients with bilateral diaphragmatic agenesis, survival rates of these patients have been reported to depend more on cardiopulmonary function and associated anomalies than the size of the diaphragmatic defect. Sweed and Puri[8] showed that associated malformations in neonates with CDH are a major factor influencing outcome in this congenital condition in addition to pulmonary hypoplasia and pulmonary hypertension. In Neville et al's study,[7] bilateral CDH was much more frequently associated with other major anomalies than unilateral congenital cardiac anomalies.

Greenwood et al[9] found that cardiovascular diaphragmatic hernia, prompting an evaluation for further anomalies particularly abnormalities, were present in 11 of 48 (23%) patients with CDH. Cardiac abnormalities included congenital heart disease, compression of a major vascular structure, cardiac malposition and abnormalities in pulmonary circulation. Mortality in infants with diaphragmatic hernia and cardiovascular abnormalities is 73%, in contrast to 27% in those without cardiac abnormalities. In Cunniff et al's study,[4] the group of children with cardiac anomalies had an increased mortality rate compared to children without cardiac defects (72% *vs.* 38%). Fauza and Wilson[5] found that hypoplastic heart syndrome was the most

common defect. In our case, we found left atrial and ventricular hypoplasia, large atrial septal defect, aortic over-ride of the septum, and pulmonary artery aplasia. Association of multiple cardiac anomalies with left pulmonary agenesis and right pulmonary hypoplasia influenced the survival of our patient.

It is possible to detect CDH prenatally by performing ultrasound examinations early in the second trimester. A much lower survival rate was found in fetuses with polyhydramnios (11%) compared to those without (55%).[10] In our case, as detailed ultrasonographic examination was not performed during pregnancy, CDH and associated anomalies were not described on prenatal ultrasound. Although likely to have been helpful in preparing the family, prenatal diagnosis would not have improved the prognosis in this case.

Tonks et al[6] found that 47% of the cases with congenital malformations of the diaphragm had additional structural or chromosomal anomalies; in their study, the infant mortality rate for these complex cases was higher. Neville et al[7] reviewed the records of 1,833 patients with CDH retrospectively; 17 had bilateral CDH. Other anomalies were diagnosed in 12 patients. Of these, 7 had cardiac anomalies, 2 had omphalocele, and 3 had chromosomal abnormalities. Among the patients with chromosomal abnormalities, 2 had Fryns syndrome and 1 had Simpson-Golabi-Behmel syndrome. There were 6 cases who survived. Our case had a normal male karyotype.

CDH is usually a sporadic, non-genetic malformation with very little risk of recurrence in subsequent pregnancies, but there have been some reports of familial recurrence in subsequent pregnancies.[11–13] Cases of familial CDH tend to be isolated defects with a low incidence (3.6%) of additional malformations, whereas associated karyotypic or multiple anomalies have been reported in nearly 50% of sporadic cases of CDH.[14] Because of this and a negative family history of CDH, we suggest that interrupted normal embryogenesis in the early developmental stages of this infant might have caused these complex anomalies. However, according to a study by Sripathi and Beasley,[15] the future offspring of parents of children with complete agenesis of the diaphragm have a significantly increased risk of having the same. Therefore, genetic counseling and detailed ultrasonographic examinations during subsequent pregnancies should be offered to women with such a history.

Agenesis of the gallbladder, with normal bile ducts, is a rare congenital condition and probably results from a failure of the gallbladder bud to develop or vacuolize *in utero*. In the literature, bilateral agenesis of the diaphragm associated with gallbladder agenesis was not described. Cunniff et al[4] examined patterns of malformation in children with congenital diaphragmatic defects and reported only 1 patient with unilateral diaphragmatic hernia associated with unilateral renal agenesis, accessory lobe of the liver and gallbladder agenesis. In this case, we present the first description of an infant with bilateral agenesis of the diaphragm associated with gallbladder and unilateral pulmonary agenesis. Whether or not there is any clinical significance or causal relationship between these anomalies needs further investigation.

In conclusion, bilateral diaphragmatic agenesis is a severe form of CDH with a poor prognosis, especially when other anomalies are also present. Although bilateral CDH is an extremely rare congenital malformation, the clinician should be mindful of this possibility.

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