

Congenital Diaphragmatic Hernia with Familial Occurrence in a Taiwanese Pedigree

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Congenital diaphragmatic hernia (CDH) is a developmental defect that accounts for 8% of all major congenital anomalies and is associated with a high mortality rate despite optimal postnatal treatment. Its etiology is uncertain. We report a case of familial CDH in a Taiwanese family. We believe autosomal recessive inheritance is the possible genetic etiology of CDH in this family. [*J Chin Med Assoc* 2005;68(10):484-486]

Key Words: autosomal recessive, congenital diaphragmatic hernia, familial

Introduction

Congenital diaphragmatic hernia (CDH) is the herniation of part of the abdominal content through a congenital defect in the diaphragm, causing varying degrees of pulmonary hypoplasia.¹ The mortality rate associated with CDH when diagnosed prenatally is up to 80% despite optimal postnatal treatment.²

The incidence of CDH ranges from 1 in 2,000 to 1 in 5,000 live births, accounting for 8% of all major congenital anomalies. 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.³⁻⁶ The risk of future siblings being affected after 1 infant has CDH is reported to be around 2%.

An analysis of available pedigree data favors a multifactorial/threshold inheritance pattern with an observed higher male-to-female ratio.⁷⁻⁹ An X-linked mode of inheritance has been suggested in a few cases of CDH with associated midline anomalies.^{6,10} There have been a small number of reports of apparent familial cases in which autosomal recessive inheritance

has been postulated.^{4,11} Here, we report 2 cases of CDH in a Taiwanese family.

Case Report

A healthy 32-year-old Chinese female had 1 first-trimester miscarriage due to a blighted ovum. There was no history of drug ingestion or consanguinity, and the detailed family history was unremarkable. Genetic amniocentesis in the second trimester of her second pregnancy showed a normal female karyotype. The baby was born at 40 weeks by spontaneous vaginal delivery and was diagnosed as having a left CDH. Despite aggressive resuscitative efforts, she died several hours later.

The third pregnancy was uneventful with the delivery of a normal male baby. In the fourth pregnancy, obstetric sonography at 20 weeks showed a left-sided CDH, with stomach filling the left chest and with mediastinal shift to the right. No associated abnormalities were detected. Genetic amniocentesis showed a normal female karyotype. The parents elected

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to continue with the pregnancy despite the poor prognosis. Polyhydramnios was noted at 29 weeks and the patient was admitted at 30 weeks of gestation with preterm labor treated with tocolytic therapy. Arrangements were made with the neonatologists and pediatric surgeons for timed delivery to enable postnatal surgery. Elective cesarean section was performed at 38 weeks of gestation. The baby weighed 3,300 g and had Apgar scores of 4 and 7 at 1 and 5 minutes, respectively. The baby was intubated immediately after birth and oxygenation with intermittent positive-pressure ventilation was maintained over the next 24 hours, but her condition deteriorated. In view of this, plans for surgery were abandoned after discussion with the parents. The baby died 24 hours after birth. No autopsy was done. Figure 1 shows the family pedigree.

Discussion

Congenital diaphragmatic defect (CDD), including CDH and diaphragmatic agenesis, is a clinical entity carrying a high mortality. The most common CDD is a posterolateral defect (Bochdalek hernia) caused by a failure in the development of the pleuroperitoneal membrane. The defect occurs with a frequency of around 1 in 2,000 births and is 5 times more common on the left side than the right. While associated karyotypic or multiple anomalies have been reported in nearly 50% of sporadic cases of CDH, cases of familial CDH tend to be isolated defects with a low incidence (3.6%) of additional malformations.^{3,7} When additional anomalies do occur, they are usually fusion defects such as neural tube defects, cleft lip and palate, and omphalocele.⁶ Cases of familial CDH, when compared with sporadic ones, show a distinct male-to-female ratio of 2:1 and a higher incidence of bilateral defects (20% vs 3%).⁷

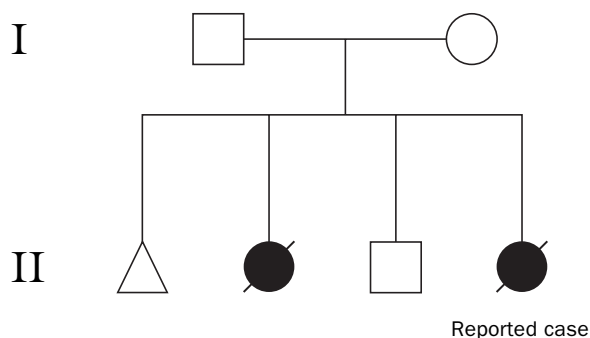


Figure 1. Pedigree of a Taiwanese family with familial congenital diaphragmatic hernia. Affected girl (●); spontaneous abortion (△); perinatal death (●).

A few cases of CDH have been reported in the Taiwanese literature, but none with familial occurrence.¹²⁻¹⁴ This is the first report of recurrent CDH in Taiwan. There have been several reports of such cases in the international literature.¹⁵ The genetic aspects of these familial cases remain unclear, but different hereditary patterns such as autosomal dominant, autosomal recessive, X-linked and multifactorial inheritance have been suggested. An imprinting mechanism might be involved in the occurrence of familial CDH.¹⁶ Because of the female predominance and a negative family history of CDH, X-linked and autosomal-dominant inheritance with incomplete penetrance are unlikely in our patients. Autosomal-recessive traits normally appear with affected babies born to unaffected parents, and there is an increased incidence of familial CDH from parental consanguinity.¹¹ After the birth of an affected child, each subsequent child has a 25% chance of being affected. We believe that an autosomal-recessive pattern is the possible genetic cause in this case.

Diaphragmatic hernia is also a feature of Fryns syndrome, a classic autosomal-recessive multiple-malformation syndrome.¹⁷ It is characterized by CDH, distal limb hypoplasia, and coarse face; other anomalies have involved the cardiovascular, genitourinary, digestive, ocular, lymphatic, and central nervous systems. Almost all infants with this condition have died at birth from pulmonary hypoplasia, and the few survivors have had severe mental retardation. In this report, neither baby had any of these anomalies except for CDH.

It is possible to detect CDH prenatally by performing ultrasound examinations early in the second trimester. Ultrafast fetal magnetic resonance imaging is also of value in predicting the outcome of CDH (low liver/diaphragm ratio).¹⁸ Predictors of poor outcome include diagnosis before 25 weeks of gestation, polyhydramnios, stomach and liver herniation into the chest, and low right lung area/head circumference ratio.¹⁹ A much lower survival rate was found in fetuses with polyhydramnios (11%) compared with those without (55%).²⁰ Amniocentesis or fetal blood sampling should be employed to rule out karyotype abnormalities such as trisomy 18, 21 and 45,X.

A genetic etiology should be suspected in cases of CDH without additional anomalies, and prenatal diagnosis should be considered in subsequent pregnancies. An overall recurrence risk of about 1% has been estimated for the siblings of a child with CDD, with the risk increasing to 10% if 2 children have been affected.^{7,10} It has been suggested that cases without other associated abnormalities may indicate a greater

risk of recurrence. Therefore, genetic counseling and detailed ultrasonographic examinations during subsequent pregnancies should be offered to women with such a history.

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