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CASE REPORT

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Familial occurrence of congenital diaphragmatic hernia

Father-to-son inheritance

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Abstract Familial occurrence of congenital diaphragmatic hernia is rare. This is only the second case of parent-to-child inheritance and the first case of father-to-son inheritance. The available data point toward a multifactorial mode of genetic transmission.

Key words Congenital diaphragmatic hernia · Familial inheritance

Introduction

It is well known that the development of a congenital diaphragmatic hernia (CDH) appears to be the result of a failure of the pleuroperitoneal folds to completely fuse [14]. The etiology of the defect remains unknown, though both non-genetic [1, 3, 8, 11, 12, 15, 22, 29] and genetic factors [2, 4–7, 10, 13, 14, 16–21, 23–28, 30] have been implicated. Polybrominated diphenyls [3], thalidomide [8], nitrofen [12], quinine [15], and phenometrazine [11, 12] have been used to induce CDH in the embryos of different species. Warkany and Roth [28] and Anderson [1] have implicated maternal dietary deficiency of vitamin A as a cause of CDH in rat fetuses. To date, no specific agent has been demonstrated to cause CDH in humans.

The genetic theories explaining the etiology of CDH are numerous and are based on familial case reports [2, 4–7, 9, 10, 13, 14, 16–21, 23–28, 30]. the incidence of familial cases is less than 2% of all cases of CDH [5, 17, 23], thus limiting the material supporting the genetic theories. The first reported familial case was published in 1916 by Makela [19]. Since then, over 30 families with over 60 affected members have appeared in the literature [20]. These reports have described identical twins (individual monozygotic and dizygotic pairs), siblings, half-siblings, a maternal uncle of affected siblings, cousins, offspring of consanguineous parents, and even two members of a set of triplets [2, 4–7, 9, 10, 13, 14, 16–21, 23–28, 30]. In 1994 Frey et al. reported the first case of paternal-to-offspring (father-to-daughter) transmission [9]. The present report is the second to document paternal-to-offspring transmission and the first report of father-to-son inheritance.

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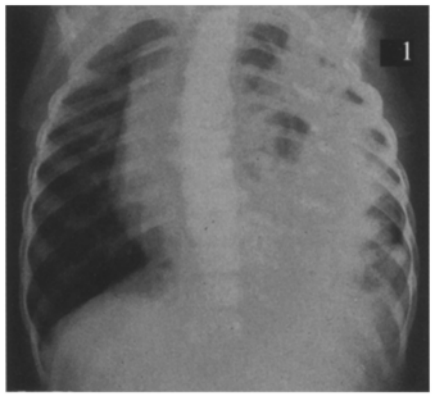
Case reports

Father

In 1954, in St. Louis, Missouri, a 3,100-g male was born after an uncomplicated 40-week gestation. He was discharged after 4 days. Because of slow feeding he was diagnosed as having a "spastic stomach." At 4 months of age severe cramping abdominal pain and vomiting occurred. A chest X-ray film (Fig. 1) demonstrated a left CDH. At exploration, the bowel was reduced via a subcostal incision and the hernia repaired. Postoperatively, the child did well and had no problems. Since this child was adopted, his parents' family and medical history were unavailable. At 35 years of age, he fathered a son with CDH. He has had three other children, two males and one female, who are completely normal.

Son

In 1989, in Denver, Colorado, a 2,450-g male was born after a 38-week gestation. A second trimester ultrasound scan revealed a left CDH. At birth he had severe respiratory distress. A chest X-ray film (Fig. 2) confirmed a left CDH. At exploration, the bowel was reduced via a subcostal incision and the hernia was repaired under tension with an abdominal muscle flap. The subcostal incision was closed with skin only. The lung was "small" in size. Postoperatively, he had a stormy course characterized by severe respiratory insufficiency. Over the next 4 years he had a repair of the incisional hernia, several central venous catheters, multiple bronchoscopies, a laparotomy for adhesiolysis, a gastrostomy, a feeding jejunostomy, a Nissen fundoplication, repair of a recurrent CDH, a tracheostomy, repair with Marlex of a second recurrent CDH, and an orchiopexy. His lung status has remained tenuous, requiring supplemental oxygen, and his weight has been consistently below the 5th percentile despite multiple feeding regimes. His three siblings, his



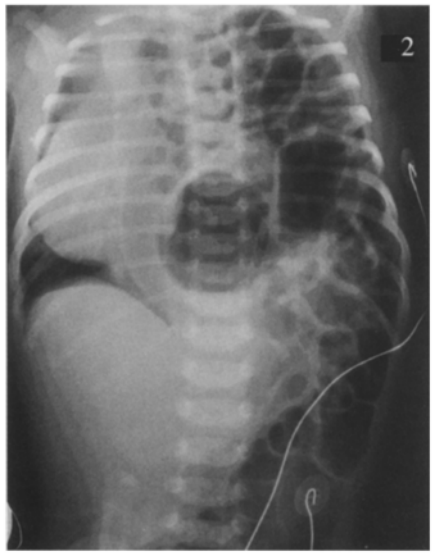


Fig. 1 AP chest film demonstrating left diaphragmatic hernia in a 4-month-old male (father)

Fig. 2 AP chest film demonstrating left diaphragmatic hernia in a newborn male (son)

mother, and his mother's family are free of any CDH or history of congenital anomaly.

Discussion

Although a CDH occurs once in every 2,000–3,000 births [23], the familial form is much less common, being estimated at approximately 1%–2% of all forms of CDH [5, 17, 23]. Familial CDH is so uncommon that it is not even mentioned in Smith's treatise on human malformations [25]. This paucity of clinical material has limited scholars' ability to elucidate the pattern of inheritance of familial CDH and provide adequate genetic counseling.

In 1968 Passarge et al. [21] postulated that familial CDH is a distinct entity with autosomal recessive transmission. Support for this suggestion came from Arad et al. [2] in a report of children of consanguineous parents. In 1979 Crane [4] provided evidence for sex-linked or autosomal dominant transmission with incomplete penetrance as the mode of inheritance. However, his explanation did not account for all of the occurrences in extended pedigrees [17]. In 1985 Toriello et al. [27] reported two siblings with pulmonary and diaphragmatic agenesis. He concluded that they represented a previously unreported autosomal recessive condition affecting either multiple developmental fields or a single complex polytopic field. Czeziel and Kovacs [5] agreed with Arad that a high rate of cousin consanguinity among parents of children with familial CDH might indicate autosomal recessive inheritance. Yet, reports of familial CDH associated with consanguinity are sparse. Nonetheless, consanguinity [27] and multiple fatal anomalies associated with CDH [5, 16, 27] may represent a separate subtype of familial CDH that is autosomal recessive in origin.

Support for multifactorial inheritance has come from the large variety of familial CDHs reported by David and Illingworth [7], Lipson and Williams [17], Schubert-Staudacher and Jauch [24], and Wolff [30]. They concluded that the male predominance in familial CDH [20], the compatibility of all the pedigrees including half-siblings [17], the paucity of consanguineous cases [2], the small number of familial CDHs relative to the sporadic CDHs [5, 20], and the heterogeneity of the anatomic findings and the associated anomalies [1–30] support the multifactorial mode of inheritance. Reports describing passage between generations have been limited to two maternal uncles of affected siblings [16, 20].

In 1994 Frey et al. [9] reported the first case of parent-to-offspring, father-to-daughter transmission. They felt that their familial CDH represented the "missing part" in the chain of support for the multifactorial inheritance of familial CDH. The present report of parent-to-offspring transmission supports Frey et al.'s opinion, eliminates the possibility that their report is a solitary chance occurrence, and adds the dimension of father-to-son transmission to the collage of familial CDHs in the literature. Currently, there are no reports of maternal-to-offspring inheritance.

Genetic counseling for parents with offspring with CDH should be tailored to the situation. Unless the offspring are of consanguineous origin or have multiple fatal anomalies, the chances of another child having CDH among first-degree relatives is 1%–2% [5, 9, 17, 23]. If there is any suspicion of autosomal recessive transmission, as in offspring of consanguineous parents or cases of multiple fatal anomalies, a 25% risk factor should be quoted [2, 21].

Since over 98% of CDHs are sporadic occurrences with no clear-cut teratogenic influence [1, 3, 8, 11, 12, 15, 22, 29], it is safe to conclude that this form of CDH is a developmental accident. Theories explaining familial CDH must include the cases of consanguineous parents [2] and multiple fatal anomalies associated with CDH [5, 27], the vast variety of familial presentations in the literature [2, 4, 5–7, 9, 10, 13, 16–21, 23–28, 30], the variable size of the defects [1–30], and the associated anomalies [7, 17, 20]. Multifactorial inheritance is the only theory that comprehensively allows for the variations found among familial CDH.

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