

Atypical Fryns syndrome: clinical, radiological and pathological findings

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Fryns syndrome is an autosomal recessive hereditary disease, including abnormal facies, small thorax with widely spaced hypoplastic nipples, distal limb and nail hypoplasia, and diaphragmatic hernia with pulmonary hypoplasia. The aim of the present report is to increase awareness of Fryns syndrome and its association with rare abnormalities such as cecal duplication cyst, horseshoe kidney and butterfly vertebra.

We report a male 20-day-old baby with congenital diaphragmatic hernia (CDH), horseshoe kidney, butterfly vertebra, cleft palate, distal finger hypoplasia, left inguinal hernia, typical facial appearance for Fryns syndrome, and cecal duplication cyst.

Fryns syndrome is the one of the most common syndromes associated with congenital diaphragmatic defect (CDH), reported in up to 10% of patients with CDH. Although no eye abnormality was seen in our patient, other findings were similar to the other typical diagnostic findings, with the exception of cecal duplication cyst and some other defects not defined before.

Key words: atypical, Fryns syndrome, duplication cyst, congenital diaphragmatic hernia, intestinal obstruction.

Fryns syndrome is an autosomal recessive, genetically determined condition with variable expression^{1,2}. Fryns et al.¹ first described this syndrome in 1979 with the major diagnostic criteria include abnormal facies (coarse face, abnormal ear shape, cleft lip, cleft palate, large mouth, microretrognathia, and broad nasal bridge), small thorax with widely spaced hypoplastic nipples, distal limb and nail hypoplasia, and diaphragmatic hernia with pulmonary hypoplasia³.

Diaphragmatic hernia is a leading diagnostic feature in Fryns syndrome, recorded in more than 80% of cases⁴. Even in the absence of diaphragmatic hernia, pulmonary anomalies are described in Fryns syndrome, especially pulmonary hypoplasia⁴.

More than 70 cases have been reported since the first report in 1979, 86% of which have been associated with an early lethal outcome⁵.

We report a baby with congenital diaphragmatic hernia (CDH), horseshoe kidney, butterfly vertebra, cleft palate, distal finger hypoplasia, left inguinal hernia, typical facial appearance for Fryns syndrome, and cecal duplication cyst.

Case Report

Our patient was a 20-day-old male baby. The mother was 31 years old. During gestation, the mother did not take any drug or toxic agent, and polyhydramnios was not detected. The parents were unrelated, and the baby was the third pregnancy, the third living offspring. The other children were healthy. He was born via cesarean section at 37 weeks of gestation with a weight of 2850 g (10th-50th percentile), length of 51 cm (50th-90th percentile) and head circumference of 31 cm (3rd-10th percentile). On the clinical examination, we detected the typical facial appearance, cleft palate, distal finger hypoplasia (Fig. 1), and left inguinal



Fig. 1. a. Typical facial appearance of patient. b-c. Cleft lip and distal finger hypoplasia are also shown.

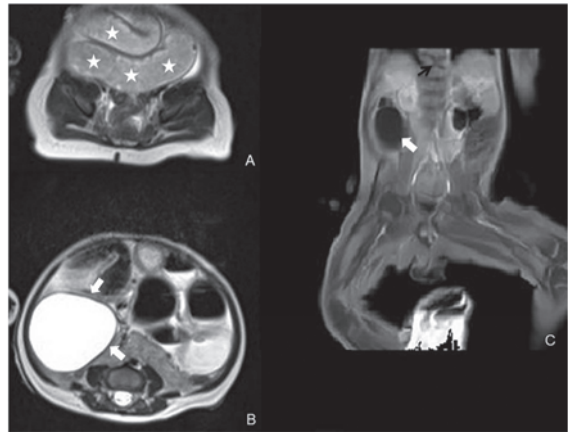


Fig. 2. a. Axial plane T2-weighted image shows small bowel dilatation (stars) and minimal free intraperitoneal fluid. b. Upper level axial plane T2-weighted images reveal cystic mass on the right side (white arrows), and horseshoe kidney can also be visualized. c. Coronal plane T1-weighted image shows cystic mass (white arrows) on the right side of the abdomen, and butterfly vertebrae (black arrow) can also be seen on the lower thoracic levels.

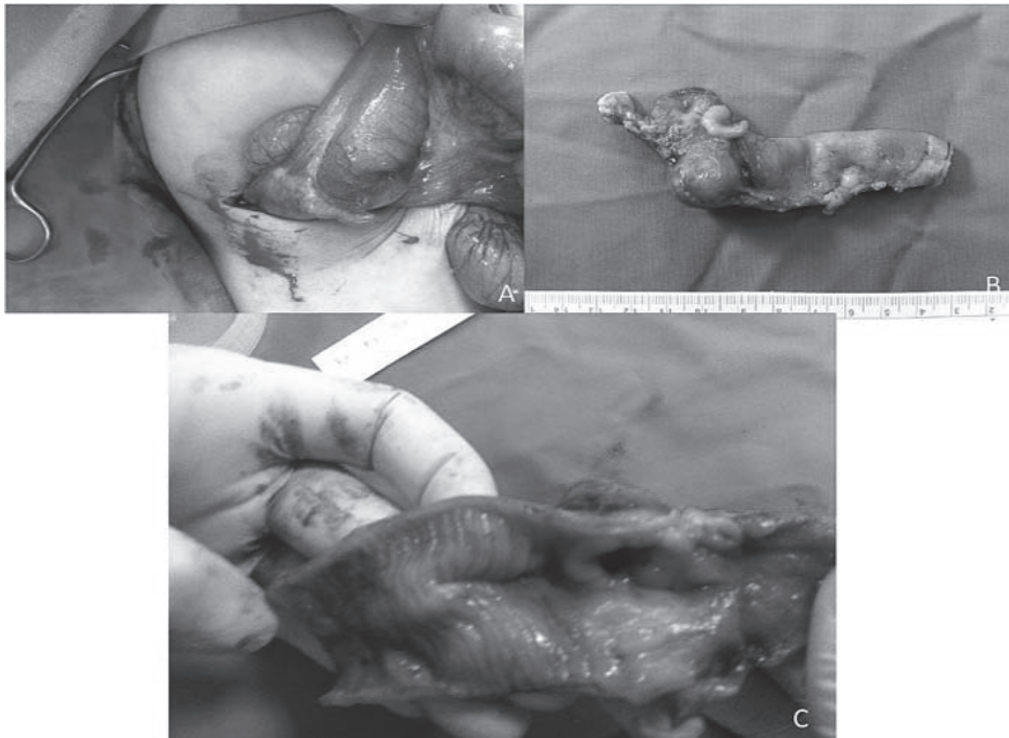


Fig. 3. Perioperative appearance of the lesion (a) and macroscopy of duplication cyst (b-c).

Table I. List of Previously Reported Fryns Syndrome Findings and Typical and Atypical Findings in our Patient, Categorized by Body Region

Anomaly localization	Type of anomalies	Typical anomalies in our patient	Atypical anomalies in our patient
Face	Coarse face, broad nasal bridge, microretrognathia, abnormal helices, cleft palate, cleft lip, choanal atresia, alveolar ridge, maxillary bone, cleft nose	Coarse face, broad nasal bridge, microretrognathia, and cleft palate	-
Orbita	Cloudy corneae, retinal dysplasia with rosettes, gliosis of the retina, thickness of the posterior capsule of the lens, irregularities of Bowman membrane, unilateral microphthalmia	-	-
Thorax	Small thorax, diaphragmatic defects, absent hemidiaphragm, absence of lung lobulation, lung hypoplasia, persistent chylothorax, extra pair of ribs	Anterior diaphragmatic defect, small thorax, lung hypoplasia	-
Cardiac	Cardiac defects, including septal defects and aortic arch anomalies	Patent foramen ovale	
Limb	Distal limb deformities, distal digital hypoplasia, osteochondrodysplasia, camptodactyly, hypoplastic nails	Distal digital hypoplasia, hypoplastic nails	-
Urogenital (rare)	Shawl scrotum, uterus bicornis, bifid uterus, hypoplastic external genitalia, renal cysts, renal cystic dysplasia	-	Horseshoe kidney
Abdominal (rare)	Duodenal atresia, pyloric hyperplasia, malrotation and common mesentery, gastroschisis, hernia	Inguinal hernia	Cecal duplication cyst
Neurological (rare)	Hydrocephaly, arhinencephaly, Dandy-Walker anomaly, macrocephaly, agenesis of the corpus callosum, progressive cerebral and brainstem atrophy, hypoplastic optic tracts beyond the optic chiasm, midline scalp defects. Scoliosis, extranumerary vertebral bodies and 13 ribs.	-	Butterfly vertebra

Table is formed from previously reported case reports findings (1-10).

hernia. Patent foramen ovale was also detected by echocardiography.

On the postnatal 20th day, plain thorax roentgenogram showed right thoracic mass and butterfly vertebra. Thoracic ultrasonography was performed, and right-sided Morgagni hernia was detected. He underwent surgery first due to Morgagni hernia. After one week, oral feeding was started, and vomiting and abdominal discomfort started concurrently. Ultrasonography revealed right upper quadrant cystic lesion, ileus and horseshoe kidneys. Magnetic resonance imaging (MRI) was performed. Small intestinal type ileus and a 4x3 cm cystic lesion in the cecum was detected (Fig. 2). Horseshoe kidney and butterfly vertebra

anomaly were also confirmed by MR (Fig. 2). The patient underwent a second operation due to intestinal obstruction secondary to the cyst of the cecum on the 40th day after birth (Fig. 3). Pathology of the specimen showed colonic mucosa inside the cystic lesion, and the diagnosis was cecal duplication cyst.

All physical and radiological findings confirmed Fryns syndrome. Karyotype analysis was normal.

Discussion

Fryns syndrome is an autosomal recessive, congenital anomaly syndrome with an incidence of one in 10,000 births^{3,6}. The rate of mortality in the lethal phenotype has changed, considering the past, and a 15% chance of survival is

reported today⁷.

Fryns syndrome is one of the most common syndromes associated with congenital diaphragmatic defect (CDH), reported in up to 10% of patients with CDH⁸. Recent studies about CDH showed genetic intervals of recurrent chromosomal aberration in humans, such as 15q26.1-q26.2 or 1q41-q42.12, as well as genes in the retinoic acid and related pathways and those involved in embryonic lung development⁹. For instance, FOG2, GATA4, and COUP-TFII are all needed for both normal diaphragm and lung development, and are likely all in the same genetic and molecular pathway⁹. It was a limitation of our report that we did not perform further evaluation showing a specific gene defect.

Cloudy cornea was initially considered as a major feature of Fryns syndrome, but it was later accepted as a minor diagnostic finding¹⁰. Although no eye abnormality was seen in our patient, other findings were similar to the other typical diagnostic findings, and some extra findings not defined previously were also present.

Classically, Fryns syndrome is characterized by distal limb hypoplasia. The spectrum of distal limb hypoplasia includes short and broad hands, short digits, short or absent terminal phalanges, hypoplastic or absent nails, and clinodactyly¹¹. Our patient showed only short digits.

Apart from these findings, our patient had some other unusual findings, such as cecal duplication cyst, horseshoe kidney, and butterfly vertebra. The findings of classical Fryns syndrome and atypical findings reported herein are listed in Table I.

Duplication cysts are rare congenital malformations, and may occur at any level from the mouth to anus¹². The terminal ileum is the most common site¹³. Colonic duplications occur in 13% of reported cases, and cecal duplications are especially rare¹⁴. About 80% these cases are detected in the first two years of life¹⁵. Herein, we report a case of intestinal obstruction secondary to a duplication cyst of the cecum and related malformations in a 40-day-old baby. To our best knowledge, concomitant cecal duplication cyst and Fryns syndrome, which are rare entities separately, has not been reported previously.

In conclusion, Fryns syndrome is an apparently

rare, autosomal recessive disorder with a high rate of stillbirth and early neonatal mortality. Prenatal recognition of lethal anomalies with routine use of imaging modalities assists in determining life-threatening findings like cecal duplication cyst.

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