

Fryns syndrome: Report of eight new cases

To the Editor:

Congenital diaphragmatic hernia (CDH) and brachytelephalangy or nail hypoplasia are cardinal manifestation of Fryns syndrome (FS; OMIM 229850),^{1,2} but it is not uncommon that there are patients with FS without CDH or nail hypoplasia in whom the diagnosis is difficult to establish. In cases of presumed FS without CDH or brachytelephalangy, the presence of another affected sibling or clinical documentation of rare anomalies previously reported in patients with FS can be diagnostically useful. We report eight new cases of FS (Table 1) to document rare anomalies such as tracheoesophageal fistula, duodenal atresia, and intraabdominal organ fusion that may be diagnostically useful in FS patients without CDH or in whom the diagnosis is unclear.

The first child was a male born to a 33-year old mother at 23 weeks of gestation who died shortly after birth. Autopsy showed a left-sided, posterolateral CDH and pulmonary hypoplasia (total lung weight 2 g). He had neck webbing, simple and low-set ears and retrognathia, hypoplasia of the distal fingers and toes, left talipes equinovarus and right talipes equinovagum, mild right hydronephrosis with pelviureteric obstruction, and bilateral cryptorchidism (normal for gestation).

The second child was born to a 24-year old mother at 38 weeks of gestation. The baby had CDH, hydronephrosis with anomalous implantation of the ureters, and Hirschsprung disease. Her medical history included severe esophageal reflux, recurrent respiratory tract infections, femoral osteomyelitis, possible seizure activity with an abnormal EEG, and an abnormal audiology exam by report. At 1 year of age, an upper respiratory tract infection resulted in respiratory depression and she died from an apneic episode. At autopsy, her weight was 7300 g (<5th percentile) and length was 68 cm (<5th percentile). Significant findings were an asymmetric depression of the right occipital bone, hypertelorism, an upturned, bifid nose, dysplastic ears, a midline cleft palate, short neck, mild pectus excavatum, and hypoplasia of all fingernails and toenails with short distal phalanges of the first fingers.

The third child was born to the same mother when she was 25 years old. In this pregnancy, a male baby was born at 36 weeks of gestation with CDH and died shortly after delivery. Postmortem examination confirmed left-sided CDH with bilateral pulmonary hypoplasia, a broad nasal bridge, dysplastic helices, micrognathia, and a cleft of the soft palate. The diagnosis of FS was made in this child despite the absence of phalangeal hypoplasia because of the previously affected sibling.

The fourth child was the first baby born to a 25-year old mother. A female infant with CDH was delivered at 33 weeks of gestation and a decision was made to withdraw care because of poor respiratory status. Examination showed coarse facies with a broad forehead, infraorbital creases, a broad and flat nasal

bridge, anteverted nares, low-set, dysplastic ears, and an everted lower lip. The neck was broad and her chest had small, wide-spaced nipples. There was brachydactyly, hypoplasia of distal phalanges of the digits, and nail hypoplasia with absence of the nails on the second and third toes. The umbilical cord had two vessels.

The fifth child was born to a 30-year old mother who had had a prior fetus affected with CDH. This pregnancy was terminated at 22 weeks of gestation because of CDH, imperforate anus, and tracheoesophageal fistula. Post mortem examination showed a male with small toenails and mild camptodactyly of the left toes. There was bilateral CDH, with both lobes of the liver positioned in a V-shape around the heart, extreme pulmonary hypoplasia, and absent lung lobation, anal atresia, cryptorchidism (normal for gestation), and fusion of the abdominal organs with hepatic tissue extending from the liver to the right testis and to the left kidney, and the left adrenal gland was fused to the left lobe of the liver.

The sixth case was a female infant born at 38 weeks of gestation with a weight of 3050 g (50–75th percentile). She had left CDH and died on the first day of life. Autopsy showed hypoplasia of both lungs, right microphthalmia with corneal clouding, macrocephaly and frontal bossing, hypoplasia of the right face with a low-set right ear, and a flat nasal bridge. Internal examination revealed aplasia of the right olfactory bulb and tract, atrophy of the right optic nerve, mild coarctation of the aortic isthmus, a patent ductus arteriosus, and pancreatomegaly due to acinar and islet hyperplasia.

The last two cases were both born to the same parents. In the first pregnancy, premature rupture of the membranes occurred at 31 weeks of gestation and all growth parameters were consistent with 34 weeks of gestation. The infant died within the first hour of life. At autopsy, findings were right CDH, severe pulmonary hypoplasia, atresia of the esophagus and proximal duodenum, renomegaly (combined weight 34.1 g; average for gestation = 13.7 g), a secundum atrial septal defect, a retroesophageal right subclavian artery, mild pancreatic islet cell hyperplasia, and a two-vessel umbilical cord. There was minor dysmorphism with posteriorly rotated ears and a small mouth. The second child born to the same parents was one of twins. She was born at 33 weeks of gestation with appropriate growth parameters, but was deceased at 24 hours of life. She had CDH, hypoplasia of the left lung (weight 10 g at 33 weeks), a patent ductus arteriosus, and a Meckel diverticulum. The fingers were long and slender with normally formed nails.

Several of these patients have rare features previously reported in FS that provide a good illustration of the remarkable phenotypic variability of this condition, including duodenal atresia, esophageal atresia and tracheoesophageal fistula,^{2,3} and hypoplasia of the olfactory nerves.^{4,5} We were unable to find

Table 1
Summary of physical findings in eight cases of Fryns syndrome

Feature	1	2	3	4	5	6	7	8
Family history of CDH		+	+		+		+	+
Diagnostic criteria								
CDH	+	+	+	+	+	+	+	+
Brachytelephalangy/nail hypoplasia	+	+		+	+			
Pulmonary hypoplasia	+		+	+	+	+	+	+
Dysmorphism	+	+	+	+		+	+	
Orofacial clefting		+	+					
Macrocephaly						+		
Thick neck/nuchal skin	+			+				
Corneal clouding						+		
Coarse facies		+		+				
Dysplastic low-set ears	+	+	+			+	+	
Broad/flat nasal bridge		+	+	+		+		
Micro/retrognathia	+		+					
Cranial asymmetry		+				+		
Small olfactory bulb						+		
Optic nerve atrophy						+		
Atrial septal defect							+	
Coarctation of aorta						+		
TOF ^a /bowel atresia					+		+	
Imperforate anus					+			
Islet cell hyperplasia						+	+	
Hirschsprung disease		+						
Renomegaly							+	
Anomalous ureters		+						
Hydronephrosis	+	+						
Organ fusion					+			
Talipes	+							
Two vessel cord				+			+	
Prenatal diagnosis	+		+	+	+		+	
AFP ^b /Triple screen	+ve							
Karyotype	46, XY	46, XX					46, XY	46, XX
Gestational age	23 w	38 w	36 w	33 w	22 w	38 w	31 w	33 w
Survival	TAB ^c	† 1 year	† day 1	†	TAB ^c	† day 1	† day 1	† day 1

^atracheoesophageal atresia; ^balpha-feto protein; ^ctherapeutic abortion.

mention of the fusions between the liver, testis, kidney, and adrenal gland, but fusions of the adrenal gland to the liver, splenopancreatic fusion, and splenogonadal fusion have each been described once in FS.⁶ These features may be useful diagnostic markers of FS in patients without CDH or for patients with CDH without nail hypoplasia.

Hirschsprung disease is a rare but notable malformation in FS with four previously reported cases.⁷ Hirschsprung disease results from aberrant migration of neural crest cells and this case supports the hypothesis that aberrant neural crest cell migration may be pathogenically important in at least some cases with FS.⁸ Further support for the importance of aberrant neural crest cell mi-

gration comes from cardiac malformations consistent with abnormal cardiac neural crest cell migration in FS, such as Tetralogy of Fallot and interrupted aortic arch.² In addition, dysregulated cell migration may be important in the pathogenesis of isolated diaphragmatic hernia. Mice with haploinsufficiency for the *slit3* gene lack the corresponding protein that acts as a guidance cue for the migration of axons and myoblasts. These knockout mice have had herniation of the septum transversum of the diaphragm.⁸

We welcome further discussion and case submission to continue the study of this phenotypically complex and heterogeneous syndrome.

ACKNOWLEDGMENT

This work was supported by REAC grant number 36248-524269, University of California, San Francisco. These studies were performed in part in the Pediatric Clinical Research Center, Moffitt Hospital, University of California, San Francisco, with funds provided by the National Center for Research Resources, 5 M01 RR-01271, U.S. Public Health Service.

Anne M. Slavotinek, MB, BS, PhD
Department of Pediatrics
Division of Clinical Genetics
University of California
San Francisco, California

Galen Schauer, MD
Department of Pathology
Children's Hospital and Clinics
Minneapolis, Minnesota

Goeff Machin, MD
Kaiser Permanente Medical Center
Oakland, California

Majed Dasouki, MD
Section of Medical Genetics and Molecular Medicine
Children's Mercy Hospital
Kansas City, Missouri

Maria E. Rueda-Pedraza, MD Frank Chiricosta, MD
Department of Pathology
Walter Reed Army Medical Center
Washington, DC

Roberta Keller, MD
Department of Pediatrics
Division of Neonatology
University of California
San Francisco, California

References

1. Fryns JP, Moerman F, Goddeeris P, Bossuyt C, Van den Berghe H. A new lethal syndrome with cloudy cornea, diaphragmatic defects and distal limb deformities. *Hum Genet* 1979;50:65–70.
2. Slavotinek AM. Fryns syndrome: a review of the phenotype and diagnostic guidelines. *Am J Med Genet* 2004;124A:427–433.
3. Ayme S, Julian C, Gambarelli D, Mariotti B, Luciani A, Sudan N, Maurin N, Philip N, Serville F, Carles D, et al. Fryns syndrome: report on 8 new cases. *Clin Genet* 1989;35:191–201.
4. Fitch N, Srolovitz H, Robitaille Y, Guttman F. Absent left hemidiaphragm, arhinencephaly, and cardiac malformations. *J Med Genet* 1978;15:399–401.
5. Cunniff C, Jones KL, Saal HM, Stern HJ. Fryns syndrome: an autosomal recessive disorder associated with craniofacial anomalies, diaphragmatic hernia, and distal digital hypoplasia. *Pediatrics* 1990;85:499–504.
6. Van Wymersch D, Favre R, Gasser B. Use of three-dimensional ultrasound to establish the prenatal diagnosis of Fryns syndrome. *Fetal Diagn Ther* 1996;11:335–340.
7. Ramsing M, Gillessen-Kaesbach G, Holzgreve W, Fritz B, Rehder H. Variability in the phenotypic expression of Fryns syndrome: A report of two sibships. *Am J Med Genet* 2000;95:415–424.
8. Yuan W, Rao Y, Babiuk RP, Greer JJ, Wu JY, Ornitz DM. A genetic model for a central (septum transversum) congenital diaphragmatic hernia in mice lacking *Slit3*. *Proc Natl Acad Sci U S A* 2003;100:5217–5222.