Fryns syndrome is a rare and most often lethal autosomal recessive complex congenital malformation. We report on a case of Fryns syndrome with “coarse facies”, broad nasal bridge, dysmorphic low-appearing ears, left cleft lip and palate, left congenital diaphragmatic hernia with lung hypoplasia, distal digital limb hypoplasia of fifth’s finger and thumbs, ureter ectopia to the persistent urogenital sinus, bilateral megaureters and hydronephrosis, agenesis of corpus callosum, hernia of the umbilical cord, Meckel’s diverticulum, malrotation, choledochal cyst and bilateral inguinal hernia. The persistent urogenital sinus with ectopic ureters and choledochal cyst were not previously described in the literature in association with other features of Fryns syndrome. These malformations add to our knowledge of the phenotype of Fryns syndrome. 

Key words: Fryns syndrome, congenital diaphragmatic hernia, non-lethal outcome.

CASE REPORT

This female baby is the first child of a 29-year-old mother and 31-year-old father, both healthy and nonsanguineous. Pregnancy was uneventful. Ultrasonography in the 29th week of gestation revealed ventricular dilatation, agenesis of the corpus callosum, cleft lip and palate, left diaphragmatic hernia, hernia of the umbilical cord, bilateral ureteral dilatation and hydronephrosis. Cordocentesis showed a normal 46XX karyotype. The child was born at 36 weeks gestation by vaginal delivery. Apgar score was 3 and 5 at 1 and 5 min, respectively. The newborn suffered significant respiratory distress requiring intubation and ventilatory support (initially 100% O₂, followed by NO). On physical examination the following abnormalities were found: cleft left lip and palate, low-set ears, boat-shaped abdomen and disten-
ded thorax (fig. 1). Chest radiographs showed left diaphragmatic hernia (fig. 2). Moreover, umbilical cord hernia was found (fig. 3). Ultrasound examination of the brain revealed absence of the corpus callosum and grade II/III° hemorrhage to the central nervous system. Abdominal ultrasonography visualized a cyst below the liver and bilateral dilatation of ureters and hydronephrosis. Echocardiography showed patent foramen ovale, small patent ductus arteriosus as the only significant cardiovascular malformations. The newborn was operated in the second day of life, the left part of the liver, spleen, stomach and bowel loops were replaced from the thoracic cavity to abdomen and the defect of the diaphragm was closed (fig. 4). At the same time the umbilical cord hernia was repaired and Meckel's diverticulum attached to the hernia sac was resected. On the 8th day of life cystoscopy was performed due to anuria and a large cystic mass in the pelvis. Ureteral ectopia to the persistent urogenital sinus was identified and both ureters were intubated. In the 7th week of life, reconstruction of the urethra, anterior wall of the vagina and uretero-cutaneostomy to the suprapubic area were performed. Mil-
Fryns syndrome – case report

Milard type plastic reconstruction of the cleft lip and palate was performed at 6th months of age, and Roux-Y hepaticoenterostomy for choledochal cyst in the 8th month of age (fig. 5, 6).

The child is currently 6 years old, developing well, although she is slightly hypotonic and presents mild mental retardation (IQ = 72) (fig. 7, 8).

DISCUSSION

Fryns syndrome is an autosomal recessive syndrome of multiple anomalies comprising diaphragmatic hernia with pulmonary hypoplasia, abnormal faces and distal limb hypoplasia.

Fig. 5. Choledochal cyst in abdominal ultrasonography

Fig. 6. Choledochal cyst – HEPIDA scintiscan

Fig. 7. Face of the child, status after Millard type plastic reconstruction of the cleft lip and palate

Fig. 8. Distal digital limb hypoplasia of thumbs and fifth fingers
plasia (2). 89 cases have been reported in the literature, revealing a wide range of variability in phenotypic expression modifying the syndrome’s earliest descriptions.

Pinar et al. reviewed 41 published cases of Fryns syndrome and added 4 more (5). The next significant elaboration was by the Congenital Diaphragmatic Hernia (CDH) Study Group. Within a database of 1833 patients with CDH, 23 patients with Fryns syndrome were identified, which accounted for 1.3% of all patients with CDH (6). We review another 21 published cases reported thereafter and add our own case. Clinical features of those patients are summarized in tab. 1.

Slavotinek concluded that CDH and distal limb hypoplasia are strongly suggestive of Fryns syndrome (29). Although diaphragmatic hernia is one of the major diagnostic criteria for Fryns syndrome, 17 cases have now been reported with no diaphragmatic defects (8, 9, 10, 16, 19). Lung hypoplasia was described in 43 of 45 cases by Pinar et al. (5) and in 17 cases of 22 the from latest literature, including our own case (7-18). Moreover, abnormal lung lobations, tracheomalatia, bronchomalatia, tracheo-esophageal fistula were described (3, 14, 15).

Craniofacial abnormalities are the most common features of Fryns syndrome (96-100% of all cases). There are “coarse face”, cleft lip and/or palate and nose with bilateral choanal atresia, nasal bridge, microretrogнатia, dysmorphic ears, cloudy appearance of the cornea, hypertelorism (1-6, 8-17, 27, 29). In our patient, unilateral left cleft lip and palate (fig. 1 and 7) were present. The next most common features of Fryns syndrome are limb anomalies: distal digital hypoplasia of some or all fingers, lack of fingernails, distal digital hypoplasia with strikingly small nails, postaxial polydactyly, clinodactyly, syndactyly. In rare cases digital hypoplasia may be very mild, as in our patient (fig. 8) (7, 14, 15).

Gastrointestinal system anomalies are less commonly described in children with Fryns syndrome. Those observed include malrotation and abnormal intestinal fixation, imperforated

<table>
<thead>
<tr>
<th>Abnormalities</th>
<th>Pinar et al. (6)</th>
<th>CDH Study Group (6), 23 cases</th>
<th>21 cases from the latest literature review</th>
<th>Our own case</th>
<th>Incidence of abnormality among children with Fryns syndrome (%)</th>
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<tr>
<td>Craniofacial features</td>
<td>43</td>
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<tr>
<td>Distal limb and nail hypoplasia</td>
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<td>Congenital diaphragmatic hernia (CDH)</td>
<td>40</td>
<td>23</td>
<td>12</td>
<td>1</td>
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<tr>
<td>Other than CDH abnormalities of the diaphragm</td>
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<td>2</td>
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<tr>
<td>Lung hypoplasia</td>
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<td>23</td>
<td>17</td>
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<tr>
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<td>36.7%</td>
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<td>0</td>
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<td>0</td>
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<tr>
<td>gastrochisis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female/male</td>
<td>20/25</td>
<td>13/10</td>
<td>11/10</td>
<td>1/0</td>
<td>45/45</td>
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<tr>
<td>Alive</td>
<td>2/45</td>
<td>4/23</td>
<td>7/22</td>
<td>1</td>
<td>14/90 = 15.5%</td>
</tr>
</tbody>
</table>

* Alkowaya FS et al. (7), Davis C et al. (8), Bartsch O et al. (9), Wilgenbus KK et al. (10), Cursiefen C et al. (11), Arnold SR et al. (12), Dix U et al. (13), Stratton RF et al. (14), Ficcadenti A et al. (15), Hanssen AM et al. (16), dog SM et al. (17), Longer JC et al. (18), Ramsing M et al. (27)
or anteriorly placed anus, Hirschsprung's disease (6 cases described in the literature) (3, 7, 8, 16), duodenal or intestinal atresia, annular pancreas, ectopic pancreatic tissue, asplenia, multiple accessory spleens, absence of gallbladder, Meckel's diverticulum. We found 3 gastrointestinal system abnormalities in our patient: Meckel’s diverticulum, malrotation with abnormal intestinal fixation, and choledochal cyst. We found no cases of association of Fryns syndrome with choledochal cyst in previous reports. To our best knowledge, this is the first report adding this defect to the phenotype of Fryns syndrome.

The following genitourinary system anomalies have been found: renal cystic dysplasia, simple cysts, renal agenesis, hypoplastic or absent uterus, bicornus uterus, duplicated uterus and vagina, uterine and cervical atresia in females, and cryptorchism, hypospadias, scrotalization of the phallus, bifid scrotum in males. Hypoplastic external genitalia, absence of clitoris, segmental renal dysplasia have also been described. Our patient presented with ectopic ureters to a persistent urogenital sinus. We have not found a similar case in the literature. We would also like to add this defect to the other possible phenotypic features of Fryns syndrome. Ectopic orifices of megaureters into the bladder neck (9) and urethra opening in the anterior vaginal wall (3) were previously reported, but not ectopic ureters to a persistent urogenital sinus.

Central nervous and cardiovascular system anomalies were not included in the original major diagnostic criteria, although they were described in the first original report by Fitz (1, 5). The list of central nervous system malformations includes: Dandy-Walker malformation, hypoplasia of optic or olphactory tracts, arrhinencephaly, agenesis of the corpus callosum, cerebellar hypoplasia, internal hydrocephalus, microcephaly, and spina bifida.

The following cardiovascular system malformations have been described: VSD, ASD, ASD+VSD, tetralogy of Fallot, interrupted aortic arch, hypoplasia of the left heart, bicuspid aortic valve, dextrocardia (5, 6, 8-12).

Additional findings belonging to the major diagnostic criteria include: broad sternal ends of clavicles (22), 11 pairs of ribs, six lumbar vertebrae, hemivertebrae C₆ and Th₁ (17). Moreover, abnormal eye findings were reported in Fryns syndrome (11, 23, 24). Pierson et al. reviewed 77 reported patients with Fryns syndrome and identified abnormal eye findings in 12 cases (23). These were: corneal clouding, anophtalmia, microptalmia, retinal dysplasia, coloboma of the iris and others. Cursifen et al. postulated that endothelial dysfunction might cause abnormal composition of anterior Descemet’s membrane and could contribute to the “cloudy cornea” in patients with Fryns syndrome (11). Retinal gliosis and “cloudy cornea” seem to occur in about one-fifth to one-third of patients (24). We confirmed anisometropic amblyopia in the left eye in our patient resulting from differences in refraction (hypermetropia). Amblyopia occlusion therapy will be confined in this child. There were no serious pathologic changes in the anterior and posterior segments of the eyes.

Omphalocoele (6, 9, 22) and gastrochisis (12) were also reported as rare findings in Fryns syndrome. Umbilical cord hernia was present in our patient (fig. 3).

Although this syndrome was reported initially as a lethal syndrome (2), there have been a number of survivors beyond the neonatal period. Van Hove et al. (24) reported a 14% survival rate, but among Pinar’s group only 2 (2/45) patients survived. The overall mortality rate within CDH Study Group was 83% (6). Improved survival is reported in more recent literature (7, 8, 9, 15, 16). Most patients with Fryns syndrome were stillborn or died soon after delivery because of diaphragmatic defects, lung hypoplasia, cardiovascular and central nervous system anomalies. Although survival of these infants is better now, mental retardation seems to be the rule in survivors. The oldest known patient with Fryns syndrome had severe mental retardation and died in status epilepticus at age of 15 years (26). Fortunately, we have noted only mild developmental delay in our patient.

Prenatal diagnosis of Fryns syndrome was first reported in 1989 with echographic evidence of polyhydramnios and congenital diaphragmatic hernia. Prenatal ultrasound examination between 16 and 36 weeks of gestation has detected structural anomalies in Fryns syndrome, such as cleft lip and palate, congenital diaphragmatic hernia, absent corpus callosum and others (3, 12, 27). The following anomalies were found prenatally in the reported child (Fryns syndrome was not
recognized, however, before birth): left congenital diaphragmatic hernia, left cleft lip, umbilical cord hernia, absence of corpus callosum, hydrocephalus and hydronephrosis with megaureters.

Fryns syndrome should be considered in every case of congenital diaphragmatic hernia. If fetal surgery for congenital diaphragmatic hernia becomes more widely available (28) Fryns syndrome should be considered before treatment in view of severe mental retardation in most survivors (3). Fryns syndrome also must be considered in cases of undiagnosed severe mental retardation, hypoplastic terminal phalanges, and coarse face.

It is a matter of discussion if the previously not reported additional anomalies found in our patient (especially choledochal cyst and ectopic ureters to a persistent urogenital sinus) are component pleiotropic manifestations of Fryns syndrome or just a coincidence. Future observations and reports of other patients should add to the support one of these possibilities.

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