CONGENITAL HIGH AIRWAY OBSTRUCTION SYNDROME (CHAOS) AS PART OF FRASER SYNDROME: ULTRASOUND AND AUTOPSY FINDINGS

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Summary: Congenital high airway obstruction syndrome (CHAOS) as part of Fraser syndrome: ultrasound and autopsy findings: Congenital High Airway Obstruction Syndrome (CHAOS) is a potential lethal condition. We describe a case report of CHAOS, with additional malformations diagnosed at 20 weeks. Autopsy findings are suggestive for Fraser syndrome (cryptophthalmos-syndactyly syndrome; OMIM 219000). The diagnosis was confirmed by mutation analysis of FRAS1.

Key-words: Congenital High Airway Obstruction Syndrome – Fraser Syndrome.

CASE REPORT

A 26-year-old nulliparous patient presented at 20 weeks for a structural anomaly scan. She was in good health and personal and family history was uneventful. Combined first trimester screening revealed a low risk for Trisomy 21 (1/23029) and Trisomy 18 (1/100000). Ultrasound showed bilateral enlarged echogenic lungs, with secondary fetal hydrops and compression of the heart, oligohydramnios and bilateral clubfeet (Fig. 1). There was no bladder filling and the kidneys could not be visualized. These findings were suggestive for a congenital high airway obstruction syndrome (CHAOS). An amniocentesis was performed. Due to the poor prognosis of the fetus, the parents opted for termination of pregnancy. The patient was primed with Mifepristone 600 mg and induced with Misoprostol 800 mg. The delivery was uneventful.

Autopsy revealed a female fetus, growth according to gestational age with multiple anomalies. There was complete blockage of the upper trachea, with very thickened cricoids and with no tracheoesophageal fistula present. There were enlarged lungs and compression of the heart and an inverted diaphragm (Fig. 2). Additionally there was fetal hydrops, low implantation of the ears, hypertelorism, and cryptophtalmos on the left side and a cutaneous syndactyly (of 4 digits).

Furthermore there was renal, ureter and bladder agenesis (which ex-
Figure 1: Ultrasound: hyperechogenic and enlarged lungs.

Figure 2: Autopsy: female fetus with closed left eye, hypertelorism, low implanted ears and hydrops of scalp and neck, enlarged lungs, compression of the heart.
plains the oligohydramnios) and agenesis of uterus and vagina. The ovaries were present. The results of the amniocentesis revealed a 46,XX karyotype. Two heterozygous sequence changes in the gene FRAS1 were identified. The c.2722+1G>A variant in intron 22 affects the conserved splice-donor and has already been found in another Fraser case (unpublished findings). The nucleotide exchange in exon 30 (c.4111C>T) creates a premature truncation codon. Both parents were carrier of one of the mutations.

**DISCUSSION**

CHAOS (congenital high airway obstruction syndrome) is a rare life-threatening syndrome, caused by an obstruction of the fetal upper airway. This obstruction can be caused by a tracheal or laryngeal atresia, but also by an extrinsic compression of the airway, such as an oropharyngeal teratoma or a cervicomediastinal lymphatic malformation. Tracheal atresia has an incidence of 1 per 50.000 newborns and consists of complete or partial absence of the trachea below the larynx, with or without a concomitant trachoeosophageal fistula (TOF) (4). The malformation is caused by nondevelopment of the 6th branchial arch during normal embryological development (5). Smith and Bain have classified laryngeal atresia into three types: type I, in which there is complete atresia of the larynx with midline fusion of the arytenoids cartilages and intrinsic muscles; type II is a supraglottic obstruction separating an incompletely formed vestibule from the infraglottic space. The latter is surrounded by a malformed dome-shaped cricoids cartilage. Type III in which there is occlusion of the anterior fibrous membrane and fusion of the arytenoids cartilages at the level of the vocal processes (5). There have been different theories to explain the cause of trachoeosophageal (TA) anomalies, like environmental factors, genetic defects which have been studied in animal models, but except for some case reports, no causal gene have been identified in human TA patients. In some case reports an association with partial trisomy 9 and 16 has been described. No sibling recurrences have been reported. The likelihood of prenatal diagnosis of a CHAOS depends on the secondary changes in the fetal lungs, and this in turn is determined by the absence or presence of a TOF. In the presence of a TOF, the lungs will develop normally and the prenatal diagnosis is impossible. Ultrasonographic characteristics for CHAOS are enlarged hyperechoic lungs, a fluid filled dilated trachea, an everted diaphragm, a compressed
heart due to the massive lungs and secondary hydrops due to inferior vena cava compression. There is usually decreased amniotic fluid and an enlarged placenta in cases of hydrops. Sometimes associated anomalies in connection to VACTERL (Vertebral anomalies, Anal atresia, Cardiac defects, TracheoEsophageal fistulae, Renal anomalies, Limb anomalies) are seen (2).

The specific signs of TA postnatally are a baby in respiratory distress with breathing movements but no appropriate air entry, no audible cry and failed endotracheal intubation. If there is a TOF, an (accidental) esophageal intubation can temporarily improve the condition of the neonate (1). Diagnosis can be made by laryngo-bronchoscopy, CT-scan and tracheotomy. If the diagnosis is made prenatally, a planned cesarean section with ex utero intrapartum treatment (EXIT) can be considered. EXIT procedure in these cases involves open fetal surgery with control of the airways by intubation or tracheostomy prior to umbilical cord clamping, enabling a placental bypass for 45-90 minutes (3, 8).

In the presence of a TOF, prenatal diagnosis is impossible and this condition is usually fatal. Despite improvement in surgical management, review of several case reports learns that only two children have survived after surgery (1).

In this case report, there was no tracheoesophageal fistula, and a high blockage, which caused enlargement of the lungs and secondary compression of the heart.

In this patient clinical findings at obduction are suggestive of Fraser syndrome (Cryptophthalmos-syndactyly syndrome). Fraser syndrome is characterized by developmental defects combining acrofacial and urogenital malformations.

The incidence of Fraser syndrome is 0.043 per 10,000 live births and 1.1 in 10,000 stillbirths

It is a clinical diagnosis: Van Haelst et al. (7) defined major criteria (syndactyl, cryptophthalmos (in which the skin covers the globe of the eye), urinary tract abnormalities, ambiguous genitalia, laryngeal/tracheal malformations, a positive family history) and minor criteria (anorectal defects, dysplastic ears, skull ossification defects, umbilical abnormalities and nasal abnormalities). Fraser syndrome is diagnosed in the presence of 3 major criteria or 2 major/2 minor criteria or 1 major and 3 minor criteria (6).

The present patient has 4 major criteria: the syndactyl, cryptophthalmos, urinary tract malformation (absent kidneys and bladder), tracheal atresia.
REFERENCES


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