Evidence for autosomal dominant inheritance in prenatally diagnosed CHAOS

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Abstract Congenital high airway obstruction syndrome (CHAOS) is a rare prenatal diagnosis consisting of a typical fetal triad of large hyperechogenic lungs, flattened or inverted diaphragms and ascites. Most cases are sporadic with unknown incidence. Before attempts of fetoscopic fetal salvage or ex utero intrapartum treatment (EXIT) are considered, additional malformations must be carefully excluded as CHAOS may be part of various monogenic conditions or chromosomal disorders. We report an unique family with autosomal dominant inheritance of CHAOS and variable expression in the affected father and two affected children. It is concluded that minor expression in one of the parents may be an important indicator for genetic counseling in CHAOS and management of future pregnancies.

Keywords Bright fetal lungs · Ex utero intrapartum treatment · Congenital high airway obstruction syndrome · Laryngeal atresia

Abbreviations CCAML: Congenital cystic adenomatoid malformation of the lungs · CHAOS: Congenital high airway obstruction syndrome · CT: Computerized tomography · EXIT: Ex utero intrapartum treatment

Introduction

The finding of congenital high airway obstruction syndrome (CHAOS) on prenatal ultrasound examination is diagnostic of a complete or nearly complete obstruction of the fetal upper airway, most likely caused by laryngeal atresia [2, 4–6, 11]. CHAOS may be part of various monogenic conditions or chromosomal disorders, but most cases are sporadic with unknown incidence [3, 7, 9, 10]. We here report a unique family with autosomal dominant inheritance of CHAOS and variable expression in the affected father and two affected children.

Case reports

Case 1 The second pregnancy of a healthy mother was uneventful until the 17th week. She was referred to our perinatal center because of the detection of several fetal ultrasound anomalies. Both lungs were abnormally large and bright. The diaphragms were inverted and ascites was also present (Fig. 1a). Amniocentesis revealed a normal male 46XY karyotype. This fetal triad was recognized as a rare, but well-described fetal anomaly called “CHAOS”, diagnostic of almost complete obstruction of the fetal upper airway. The boy was born at 35 weeks’ gestation, 3 weeks after preterm premature rupture of the mem-
Arterial umbilical pH was 7.31. Immediate laryngoscopy confirmed the total glottic obstruction. He was treated successfully by emergency tracheostomy. A secure subglottic airway was established within 2 min after birth without an ex utero intrapartum treatment or so called EXIT procedure. At 5 min, 400 ml of ascitic fluid was evacuated by paracentesis. Transcutaneous oxygen saturation increased gradually to more than 95% at 7 min. Apgar scores were 1, 6 and 8 at 1, 5 and 10 min of life, respectively. Clinical examination revealed no dysmorphic features apart from a broad thoracic cage and a “prune belly” abdominal appearance after the paracentesis. The baby was easily weaned to continuous positive airway pressure ventilation through the airway canula over the first few days with a fractional inspiratory oxygen concentration of less than 30%. Thoracic X-rays showed that large hyperlucent lung fields and inverted diaphragms were still present (Fig. 1b). The upper airway CT scan revealed a long gap at the cricoid level (Fig. 2a), which was subsequently confirmed by surgical exploration of the upper airway. Long-term laryngeal reconstruction was considered to be functionally and ethically unfeasible, and the infant was allowed to die in accordance with the parents’ wishes. Postmortem examination did not reveal any other significant anomaly with the exception of the broad laryngeal atresia.

Case 2 The next pregnancy was uneventful except for a significant polyhydramnios. No further prenatal diagnostic examination was performed in the referring hospital and the girl, born at 38 weeks’ gestation, was transferred to our neonatal intensive care unit because of congenital stridor with severe hypercapnia (pCO₂ 85 mmHg). Direct laryngoscopy revealed a subtotal laryngeal atresia with only an extremely small posterior fistula left for air entry. CT scan confirmed this pinpoint posterior hole (Fig. 2b). The baby was urgently tracheotomized. The canula was subsequently adapted for growth, and reconstructive surgery is planned. Cytogenetic analysis was normal in both infants. Because laryngeal webs and CHAOS have been reported in the velocardiofacial syndrome, Fluorescence in situ hybridization (FISH) analysis was performed, but there was no sign of a submicroscopic 22q11 deletion.

During a repeated family history the hoarse-voiced father informed us that during his first years of life he was treated for so-called “chronic croup” by tracheal cannulation. Recent indirect laryngoscopy still revealed a partial subglottic webbing without functional repercussion, suggesting that he is also mildly affected by the condition.

**Discussion**

The typical triad of fetal diagnostic criteria for CHAOS are easily visualized on ultrasound, as well as on magnetic resonance imaging. If an invasive fetal or perinatal therapeutic procedure is considered, the latter technique is probably superior for the more precise evaluation of the upper airway patency. Bilateral bright lungs due to CHAOS should be differentiated from the exceptionally bilateral presentation of congenital cystic adenomatoid malformation of the lungs (CCAML). The amount of amniotic fluid may be helpful, since CHAOS with total obstruction usually presents with oligohydramnios.

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**Fig. 1** a. Fetal ultrasound showing the typical triad of CHAOS: bilateral bright lungs (LL), inverted diaphragms (I) and ascites (A). b. Postnatal thoracic X-ray showing the corresponding large hyperlucent lungs, inverted diaphragms and tracheal canula (T).

**Fig. 2** a. Sagittal reconstruction CT image showing the large laryngotracheal gap in case 1 (black arrows). b. Identical image showing a pinpoint posterior laryngeal hole in case 2 (white arrow).
whereas polyhydramnios is present in most cases of bilateral CCAML [11].

Few infants have been salvaged by an ex utero intrapartum treatment (EXIT) procedure, but longterm survivors without brain damage or permanent tracheostomy are extremely rare [2, 5, 6]. From this single experience, we conclude that in selected cases emergency neonatal tracheostomy can be done by an experienced senior head-and-neck surgeon within 2 minutes after birth without the need of a longer fetoplacental perfusion time by a formal “ex utero intrapartum treatment”. We found it necessary to deliver the entire fetus to improve immediate airway access, still safely achieving a high airway procurement success without increasing the risk of maternal complications. Preciado et al. [12] came to a similar conclusion in a series of newborn infants with severe congenital airway obstruction. Kohl et al. [10] showed that percutaneous fetoscopic and ultrasound-guided decompression of the fetal trachea is feasible and may permit normalization of hemodynamics in hydropic human fetuses with CHAOS from laryngeal atresia.

Most cases of typical CHAOS with complete airway obliteration are sporadic, but the incidence is unknown. Additional malformations should be excluded as CHAOS may be part of various monogenic conditions such as Fraser syndrome [10] and short-rib polydactyly syndrome (SRPS) [3] or chromosomal disorders such as a deletion of the short arm of chromosome 5 (“Cri du Chat” syndrome) [9] and a microdeletion of the long arm of chromosome 22 (22q11.2- or velocardiofacial syndrome) [7]. Baker and Savetsky described a congenital, but only partial atresia of the larynx in an affected mother and two of her children in whom tracheostomy was performed within minutes after birth [1]. Our family shows further evidence for autosomal dominant inheritance with variable expression of CHAOS in a mildly affected father and 2 affected children. Minor expression in one of the parents may thus be important for genetic counseling in CHAOS and management of future pregnancies. Although our multidisciplinary perinatal approach was successful without EXIT procedure, as far as immediate and safe neonatal airway patency was concerned, outcome on the long run was considered ethically and functionally unfeasible. Perinatal management of the airway, particularly in regard to long-term reconstruction, in children with CHAOS remains indeed very complex and challenging [8].

References