Case Report

Otocephaly (Agnathia)-Situs inversus complex with bilateral absence of mandibular nerves

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ABSTRACT

Otocephaly is a rare lethal neurocristopathy of first branchial arch, characterized by agnathia (agenesis of mandible), ventro-medial displacement and midline fusion of external ears (synotia), microstomia (small mouth) and aglossia (absence of tongue) or microglossia (small tongue). This anomaly is a consequence of failure of migration of neural crest cells from hind brain which contributes to the development of maxillary and mandibular prominences of the first arch. A female fetus of 28 weeks gestation, spontaneously aborted, was received for autopsy. On external examination, the fetus exhibited ventrally placed malformed ears in the neck region, agnathia, microstomia and microglossia. Internal examination revealed situs inversus totalis, atrial septal defect and bilateral absence of mandibular nerves. Our case is unique, and here rendered for publication, due to association of otocephaly with situs inversus totalis in the absence of holoprosencephaly. We discuss current perspectives, literature review and molecular mechanisms implicated in otocephaly complex patterning.

Keywords: Otocephaly, Agnathia, Synotia, Microglossia, Situs inversus totalis, Mandibular nerves

INTRODUCTION

By accepting the shelter of the uterus, the fetus also takes the risk of maternal diseases or malnutrition, and of biochemical, immunological and hormonal adjustments: which are a frequent cause of fetal and neonatal morbidity and mortality. This can be a cause of concern to mother, family and society too! Birth defects can be detected prenatally by various investigations. These can be expedient in early counselling of eligible couple and further management of unborn patient and mother. These anatomically abnormal babies with cephalic malformations draw more attention and interest.

Otocephaly is a rare lethal non-familial, neurocristopathy of the first branchial arch. The “oto” in the name refers to the relationship of the ears to the face, in this deformity. This anomaly is considered lethal due to severe respiratory dysfunction. The primary feature in this cephalic disorder is agenesis of the mandible (agnathia). Other dysmorphologic sequelae include ventro-medial displacement and midline fusion of the external ears in the neck region (synotia), microstomia (small mouth) and aglossia (absence of tongue). Here we detail a rare case of otocephaly associated with situs inversus totalis on fetal autopsy. We also review the literature on molecular mechanisms implicated in otocephaly complex patterning.
CASE REPORT

A 29 year old primi gravida with polyhydramnios delivered at 28 weeks of gestation, a female baby with severe facial malformations. There was no family history of consanguinity or congenital malformations. There was no maternal history of Hypertension, diabetes mellitus, asthma, recent infection or any exposure to teratogens. The baby showed multiple facial anomalies including absence of the mandible, microstomia and extremely low-set ears. This fetus expired immediately due to severe airway dysfunction and was sent for autopsy for detailed study.

External examination revealed agnathia, microstomia and ventrally displaced ears. Ears were extremely low-set and fused in the midline of the neck (synotia). External auditory meatus was not patent. Other facial features included: hypertelorism, down-slanting palpebral fissures and microcephaly (Figure 1A & 1B).

Figure 1 A & B: External features.

Figure 2 A & B: Choanal atresia and absent auditory tube.
Examination of oral cavity showed narrow palate and small rudimentary tongue (microglossia). Mid sagittal section of head and neck was made to examine nasal cavity, oropharynx and larynx. Nasal cavity showed normal medial and lateral walls. There was choanal atresia. There was no auditory tube opening in the nasopharynx (Figure 2A & B). Larynx, trachea and oesophagus were normal. Examination of the middle ear cavity revealed absence of ear ossicles.

Internal examination of thoracic cavity revealed hypoplastic thymus. There was mirror-image...
dextrocardia, i.e. the positions of heart chambers and major vessels were exactly the reverse of the normal arrangement. The apex of the heart was on right side (Figure 3A). The morphological right atrium was positioned on the left side and received superior venacava and inferior venacava. Arch of azygos vein was on the left side and drained into superior vena cava (Figure 3B). The left atrio-ventricular orifice was guarded by the tricuspid valve. The morphological left atrium and its appendage were positioned on the right and posterior aspect of the heart, receiving two pulmonary veins one on each side. The right atrio-ventricular orifice was guarded by the bicuspid valve. The morphological right ventricle (presence of moderator band and coarse trabeculae) was positioned on left side and committed to the pulmonary trunk. The pulmonary trunk was bifurcated into right and left branches and placed anterior and to the right of arch of aorta (Figure 3C). The morphological left ventricle (presence of fine trabeculae) was positioned on right side and committed to the ascending aorta. The ascending aorta was placed posterior and to the left of pulmonary trunk. The ascending aorta continued as the arch of aorta from left to right (right-sided aortic arch) and further continued as right-sided descending aorta. The right pulmonary artery was connected to descending aorta through right-sided ductus arteriosus (Figure 3D). The branches of arch of aorta from left to right were: left brachiocephalic trunk (divided into left subclavian and left common carotid arteries), right common carotid and right subclavian arteries. There was a large atrial septal defect (Figure 4). Inter ventricular septum was normal.

The right and left lungs were not lobated; however right lung had a partial fissure (Figure 5A & 5B).

The left dome of diaphragm was placed higher than the right dome.

Abdominal examination showed situs inversus totalis. The left lobe of liver was larger than the right lobe and the gall bladder was on the left side (Figure 6A). Stomach and spleen were placed on the right side (Figure 6B). Appendix was in the left sub-hepatic region. Convexity of duodenal ‘C’ loop was on to the left side and the tail of pancreas was on the right side (Figure 6C). The sigmoid colon and rectum were placed on the right side. Adrenal glands and urinary system were normal. Uterus was levo-positioned (Figure 6D).

Brain was appropriate and normal for the gestational age except for hypoplastic cerebellum (Figure 7). Trigeminal nerve showed bilateral absence of mandibular division and on left side ophthalmic division was also absent (Figure 8A & 8B).

X-ray skull showed agenesis of mandible, hypoplasia of maxilla and abnormal cervical vertebrae (Figure 9A, 9B & 9C).
Figure 5 A & B: Lobation defects of right and left lungs.

Figure 6A: Left-sided gallbladder and appendix; 6B: Stomach and spleen are on right side; 6C: ‘C’ loop of duodenum on left side; 6D: Levo-positioned uterus.
DISCUSSION

Otocephaly is a rare lethal syndrome spectrum ranging in severity from micrognathia as in Robin sequence to cyclopia-holoprosencephaly complex. It has been considered as the most extreme form of the first and second arch defects. The estimated prevalence of otocephaly is less than 1 in 70,000 births. The characteristic features of otocephaly include agnathia, synotia, microstomia with persistent buccopharyngeal membrane and aglossia or microglossia. Holoprosencephaly is the most commonly associated anomaly with otocephaly but other associations include cardiovascular, skeletal, situs inversus totalis and genito-
urinary anomalies. The anatomic sub classification of otocephaly-agnathia complex includes four types: 1. Isolated agnathia, 2. Agnathia with holoprosencephaly, 3. Agnathia with situs inversus and visceral anomalies, 4. Agnathia, holoprosencephaly, situs inversus and other visceral anomalies. Agnathia-holoprosencephaly is relatively more common and associated with multi-system abnormalities including situs inversus. The present case under discussion is of type 3 otocephaly.

Figure 9 A & B: X-Ray of the fetus – Antero-posterior (AP) & Lateral views; 9C: X-Ray – AP view of the head and neck.

Agnathia was first reported by Ahfeld in 1882. Later many cases of agnathia reported in literature were commonly associated with holoprosencephaly and situs inversus totalis. Very few cases reported isolated situs inversus totalis with otocephaly agnathia complex. Pauli et al reported two cases of agnathia-holoprosencephaly syndrome associated with cardiac anomalies, stage-2 malrotation of the gut with a common mesentery, and a hypoplastic right kidney. One case had complete agenesis of the olfactory bulbs. Ozden et al reported a case of
agnathia and synophthalmia with frontal proboscis, aglossia, situs inversus totalis, alobar holoprosencephaly and agenesis of the corpus callosum. Ears were extremely lowset but not fused in midline of neck. Schiffer et al reported a sporadic case of agnathia-otocephaly complex with agnathia, hypoplastic maxilla, low-set fused ears in the midline, microstomia with persistence of the buccopharyngeal membrane, a small tongue, anal atresia and pes equinovarus. Puvabanditsin et al reported two unrelated infants with otocephaly, agnathia, microstomia, cleft palate. One infant had pulmonary hypoplasia. The latter infant also had holoprosencephaly, situs inversus, and transposition of the great arteries. Faye-Petersen et al reported five cases of otocephaly. Among them, one had holoprosencephaly and situs inversus. Celik et al reported a female infant, born of consanguineous parents, with otocephaly who died shortly after birth from respiratory distress. Post-mortem examination showed down-slanting palpebral fissures, synotia, a hypoplastic oropharynx with a blind-ended and small stoma, hypoplastic and retro-positioned tongue, hypoplastic and dysmorphic larynx and epiglottis, agenesis of the tracheo-oropharynx connection, and a blind-ended proximal trachea. Agnathia was confirmed by cranial imaging. Other anomalies included open and atretic external auditory canals, tracheomalacia, bilateral pulmonary hypoplasia, and an atrial septal defect. Almost all cases were associated with polyhydramnios. Our case also had polyhydramnios. Schmitzer CL et al reported two cases of otocephaly with hypertelorism, microcephaly, agnathia, pulmonary hypoplasia. Second case also had multiple skeletal anomalies, bilateral renal agenesis, persistent cloaca, rectal atresia, common oropharyngeal cavity, right adrenal agenesis with small dysplastic left adrenal, absent pituitary gland, bicornuate uterus ending in two blind vaginal tubes, persistent left superior vena cava and large supracristal, ventricular septal defect with pulmonary aortic window.

The case under discussion had hypertelorism, down slanting palpebral fissures and microcephaly, agnathia, hypoplastic maxilla, microstomia, microglossia and ventrally displaced lowset fused ears in the midline of neck, narrow palate, choanal atresia, common oropharyngeal cavity, hypoplastic thymus, atrial septal defect and pulmonary lobarion defects, in addition to situs inversus totalis.

Embryologically, the face, neck, nasal cavities, oral cavity, tongue, larynx and pharynx develops from the branchial arches. The primary defect in the development of otocephaly-agnathia complex is a consequence of failure of migration of neural crest cells from the hind brain which will contribute to the development of maxillary and mandibular prominences of first arch. Mandible, muscles of mastication, ear ossicles (malleus and incus) are derivatives of the mesoderm of first branchial arch. Mandible forms the main component of first arch cartilage and keeping pace with its growth, guides its early morphogenesis. The downward and ventral displacement of ears and microstomia in otocephaly are secondarily due to the failure of spatial separation of mandible. First arch muscles are supplied by mandibular nerve. This explains the reason for absent mandibular nerve and ear ossicles along with agnathia in the present case.

Animal models suggest that otocephaly results from heterogeneous developmental defects. Both genetic and environmental factors play an important role in the occurrence of otocephaly. Teratogenic effects of several agents such as strepigrin antibiotic and trypan blue have been reported to cause otocephaly. Ibba RM et al suspected that, theophylline could be a cause of otocephaly. Hide T et al identified one significant locus, Otmf18, between D18Mit68 and D18Mit120 on chromosomes 18, linked to the mandibular phenotype (LOD score 3.33).

Chromosomal and molecular studies explain the etiopathogenesis of otocephaly. Pauli et al, suggested an autosomal recessive etiology of the agnathia-holoprosencephaly syndrome and demonstrated a balanced translocation in the father of the affected individuals and an unbalanced translocation in the second of the 2 sibs by prometaphase chromosome studies. One of the breakpoints was at 18p, which is known to be a locus for holoprosencephaly. Krassikoff and Sekhon described agnathia-holoprosencephaly in 3 infants, all offspring of a man who, had a balanced t(6;18) translocation. All 3 infants were thought to have duplication of 6p and monosomy of 18p. Erlich et al suggested autosomal dominant inheritance and raised the possibility of a defect in the OTX2 gene as the basis of the dysgnathia syndrome. Schiffer et al and Sergi et al identified a heterozygous loss-of-function mutation in the PRRX1 gene in a fetus with agnathia-otocephaly complex. The PRRX1 gene was selected for sequencing because of its known role in mandibular-facial development. Celik et al identified a homozygous loss-of-function mutation in the PRRX1 gene in a female infant, born of consanguineous parents, with agnathia-otocephaly complex.

The first branchial arch patterning is influenced not only by the complex interplay between the genes and gene products but also by the temporal and spatial relationships between them. The absence of bone morphogenic protein 4 (Bmp4) antagonists, Chordin and Noggin, leads to a spectrum of mandibular hypoplasia. Liu et al demonstrated differential effects of Bmp4 on fibroblast growth factor 8 (FgF8) expression in the proximal and distal mandible. Twisted gastrulation protein (Tsg) has been shown to have differential effects on the function and activity of Bmp4 and its role on first branchial arch patterning. Recent studies with proteomics identified 21 proteins expressed in the chick embryo during the rapid growth phase of first branchial arch development. Further characterization of these and
other molecular interaction will greatly affect the understanding of craniofacial patterning.  

To conclude, otocephaly-agnathia-situs inversus complex is a rare syndrome and most commonly associated with holoprosencephaly. It rarely presents as an isolated situs inversus totalis as in our case. Bilateral absence of mandibular nerves substantiates the agenesis of first branchial arch in otocephaly-agnathia complex. Early diagnosis of this syndrome is made by fetal three dimensional (3D) ultrasonography and MRI. This condition has to be differentiated from other first arch syndromes like Treacher Collins syndrome, Pierre Robin syndrome, Goldenhar syndrome, Nager syndrome and the Robin sequence. Prognosis is poor in otocephaly-agnathia due to severe respiratory failure.

REFERENCES


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