CASE REPORT

Cyclopia: isolated and with agnathia–otocephaly complex

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SUMMARY

Cyclopia is a rare form of lethal holoprosencephaly (HPE) due to incomplete cleavage of prosencephalon during embryogenesis, leading to failure of the orbits of the eye to divide into two cavities. We report two cases, one with cyclopia and another case of cyclopia with agnathia–otocephaly complex (AOC). AOC (also known as agnathia–microstomia–synotia syndrome) is a rare lethal congenital malformation of the first branchial arch characterised by the association of agnathia (agenesis of mandible) or mandibular hypoplasia, melotia (anteromedial malposition of ears), microstomia (small mouth), aglossia or microglossia (absent or rudimentary tongue). These two reported cases had in common a single eye and alobar HPE. The first case was live born and the second stillborn. Both mothers did not have antenatal care.

BACKGROUND

Cyclopia and agnathia–otocephaly complex (AOC) are extremely rare embryological malformations. Knowledge of these malformations is useful for neonatologists/paediatricians and obstetricians

when faced with these cases at birth, especially in the absence of antenatal care.

CASE PRESENTATION**Case 1: cyclopia**

A term, female baby was born to a 27-year-old mother, G4P3, by emergency lower segment cesarean section (LSCS), indication being pre-eclampsia, after an unbooked pregnancy. The parents were non-consanguineous and there was neither maternal history of diabetes in past pregnancies nor medication intake. She had a previous preterm baby (30 weeks) who passed away in neonatal period due to respiratory distress syndrome.

The baby at birth had some gasping efforts and the attending obstetrician and paediatrician decided not to resuscitate because of major facial malformations. On examination, the infant had cyclopia, proboscis and low-set ears (figure 1). Jaw and chin were normal. An examination of the oral cavity revealed normal gums, tongue and laryngeal inlet. No cleft palate was noted. Head was large and the upper helix of the ears were prominent. The head circumference was 41 cm and weight 2200 g. Trunk, abdomen, spine, genitalia and limbs were normal. An infant feeding tube could be passed down to the stomach. A bedside cranial ultrasonography revealed a large monoventricle outlined by fused thin rim of cerebral hemispheres and fused thalami, consistent with a diagnosis of alobar holoprosencephaly (HPE). An ultrasound of the abdomen showed normal abdominal situs and echocardiography showed a poorly contractile heart with normal situs. The baby was born with feeble heart-beat and gasping respiratory efforts and passed away shortly after birth. Karyotyping and post-mortem examination were declined by the family for religious reasons.

Case 2: cyclopia with AOC

A female 32-week-old stillborn fetus weighing 1920 g was born to a 16-year-old single mother by normal vaginal delivery. The mother did not have antenatal care. There was a history of failed attempt to abort using indigenous medicines at 14 weeks of pregnancy. Physical findings included cyclopia, agnathia, microstomia, melotia and a probosciform frontal soft mass noted below the eyes (figure 2). No bony parts could be palpated in the jaws. Limited examination of the oral cavity revealed a small mouth and absent gums and tongue. The insertion of a feeding tube was unsuccessful beyond

Figure 1 Cyclopia, proboscis and low-set ears.

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Figure 2 Agnathia–otocephaly complex with cyclopia, agnathia, microstomia and melotia.

the pharynx. On probing the external auditory meatus, bilaterally, the probe ended blindly. The neck was webbed, with rugous thickening of the skin. Cranial ultrasonography revealed a dilated monoventricle with a thin rim of cerebral hemisphere around it (figure 3) and a limited echocardiography revealed a normal situs. No other anomalies were noted on the torso or extremities. Karyotype was normal. No consent could be obtained for postmortem examination. The clinical features and cranial sonography were consistent with a diagnosis of cyclopia with AOC.

OUTCOME AND FOLLOW-UP

Case 1 was alive only for a few minutes and the case 2 was still-born.

DISCUSSION

As described above, both patients had cyclopia and alobar HPE. The former additionally had a true proboscis above the midline eye and the latter agnathia, melotia and microstomia. Despite

Figure 3 This coronal cranial ultrasound image of case 2 shows the presence of a single ventricle (monoventricle) with fused central thalami consistent with the diagnosis of alobar holoprosencephaly.

some similarities, they had very different appearance and aetiologies which will be discussed here.

Prevalence

The global prevalence rate of Cyclops was reported as 1 in 100 000.¹

AOC is a rare anomaly reported in less than 1 in 70 000 births.²

Aetiology of HPE

HPE is caused by incomplete development and separation of the midline central nervous system (CNS) structures. The forebrain divides into two cerebral hemisphere around the fourth to sixth week of embryonic stage. The failure of this separation leads to different forms of HPE.³ There are three classical forms of HPE: lobar, semilobar and alobar. Alobar HPE is the most severe form of HPE, which presents with cyclopia and is incompatible with life. Another variant of HPE known as middle interhemispheric fusion (syntelencephaly) exists, in which there is an abnormal midline connection of the cerebral hemispheres in the posterior frontal and parietal regions, with interhemispheric separation of the basal forebrain, anterior frontal lobes and occipital regions.^{3,4}

DeMyer *et al* commented that adequate attention to facial anomalies can predict the brain status. They humorously proposed that 'The face predicts the Brain'.⁵ DeMyer *et al* classified the facies of HPE into five categories.⁶

1. Cyclopia (the most severe form) in which a single eye is located in the area normally occupied by the root of the nose, and arhinia (missing nose) with a proboscis (a tubular-shaped nose).
2. Ethmocephaly (the least common facial anomaly) in which a proboscis separates closely set orbits.
3. Cebocephaly which is characterised by orbital hypotelorism and proboscis-like nose with no median cleft lip.
4. Median cleft lip with premaxillary agenesis, having orbital hypotelorism and flat nose.
5. With median philtrum–premaxilla anlage, associated with orbital hypotelorism and flat nose. This is the least severe of the facial anomalies.

Types I to IV are associated with alobar HPE, whereas type V usually presents with semilobar or lobar HPE.

HPE has been linked to several genetic abnormalities, especially trisomies, trisomies 13 and 18.¹ SHH, ZIC2, SIX3, TGIF and several other genes have been identified as a cause of HPE.⁷ Environmental factors such as maternal diabetes, maternal use of alcohol, diphenylhydantoin, aspirin, misoprostol, methotrexate, retinol and cholesterol-lowering agents have been implicated but causal relation is not proven.^{8–15} It can also be associated with syndromic disorders as shown in table 1.¹⁶

Aetiology of AOC

AOC is the most severe form of the first branchial arch anomalies. It is a defect of blastogenesis resulting in failed mesenchymal migration of the maxillary prominence and atrophy in the development of the mandibular prominences.¹⁷ This complex has at least four different types: (1) isolated agnathia, (2) agnathia with HPE, (3) agnathia with situs inversus and visceral anomalies and (4) agnathia, HPE, situs inversus and other visceral anomalies. Case 2 discussed in this report is most likely a type 2 AOC.

Cytogenetically, balanced translocation between chromosomes 18 and 6 and mutations in OTX2 PRRX1 gene were reported in AOC. Most cases are sporadic but autosomal dominant and recessive modes of inheritance have been reported. [OMIM 202650]

Table 1 Syndromic HPE

Autosomal dominant	Autosomal recessive
Pallister-Hall syndrome	Pseudotrisomy 13 syndrome
Rubinstein-Taybi syndrome	Smith-Lemli-Opitz syndrome
Kallmann syndrome	Meckel syndrome
Martin syndrome	Genoa syndrome
Steinfeld syndrome	Lambotte syndrome
Hartsfield syndrome	Hydrolethrus syndrome
	Facial clefts and brachial amelia
	Autosomal dominant versus multifactorial
	Microtia-antonia and other anomalies
	Holoprosencephaly-agnathia spectrum disorders

Clinical features of HPE

The following findings are reported in HPE. [OMIM 236100]

Head: ethmocephaly, cebocephaly, microcephaly
 Face: facial cleft, premaxillary agenesis, midfacial hypoplasia
 Eyes: cyclopia, ocular hypotelorism, colobomata, microphthalmia
 Nose: arrhinia, blind-ending proboscis, agenesis of nasal bones
 Mouth: median cleft lip/palate
 Teeth: central incisor
 CNS: seizures, hypotonia, agenesis of corpus callosum, cerebellar hypoplasia, neural tube defects, absent interhemispheric cleavage, fused thalamus and single ventricle in alobar HPE, posterior interhemispheric fissure with rudimentary cerebral hemispheres and single ventricle in semilobar HPE, clear interhemispheric fissure and two lateral ventricles in lobar HPE.
 Endocrine: pituitary agenesis, hypophyseal agenesis, hypothalamic dysfunction, hypoplastic adrenal glands, diabetes insipidus.

Clinical features of AOC

The following are findings reported in AOC cases. [OMIM 202650]

Head: otocephaly
 Face: mandibular hypoplasia or agenesis
 Ears: synotia, ear anomalies
 Eyes: synophthalmia
 Nose: frontal proboscis
 Mouth: microstomia, microglossia, aglossia, cleft palate, hypoplastic oropharynx
 Larynx: hypoplastic epiglottis, hypoplastic larynx, trachea-oro-pharynx connection agenesis
 Airways: blind trachea, tracheomalacia
 Abdomen: situs inversus
 CNS: HPE, agenesis of corpus callosum

Antenatal diagnosis

The following prenatal tests should be offered for high-risk pregnancies: (1) molecular genetic testing, chromosomal analysis or chromosomal microarray. These tests are of varying utility, depending on whether there is a known genetic or chromosomal defect in the family.¹⁶ (2) Foetal ultrasound examination and foetal MRI. Ultrasound with or without MRI can detect HPE as early as 9 weeks of gestation.¹⁸ The diagnosis is suggested by the findings such as cyclopia, cebocephaly, ethmocephaly, hypotelorism, proboscis, median cleft lip, single ventricular cavity, thalamic fusion, absence of median structures and microcephaly. Prenatal diagnosis of AOC is more challenging and the diagnosis is usually made later in the pregnancy. However, use of three-dimensional ultrasound technique can be helpful to get an

earlier diagnosis by identifying agnathia and synotia.¹⁹ In both the reported cases, the mothers did not have antenatal care and hence no prenatal imaging was done.

Prognosis

Infants with alobar HPE die within days after birth.¹⁹ Most of the infants with severe forms of otocephaly are stillborn or dead shortly after birth. Cases with severe agnathia without lethal malformation have been reported to survive until adulthood with multidisciplinary support.²⁰

Genetic counselling

Both HPE and AOC can be sporadic, autosomal dominant or recessive in inheritance. Odent *et al* concluded after segregation analysis in 79 nuclear families that the transmission of non-syndromic HPE is compatible with an autosomal dominant mode of inheritance.²¹ If the parental carrier state of known genetic defects is confirmed, the risk of recurrence is higher. Therefore, genetic testing should be offered to parents and counselling is based on the specific cause of the disorder.

Learning points

- Cyclopia is a lethal malformation.
- Antenatal diagnosis is possible for both holoprosencephaly (HPE) and agnathia-otocephaly complex (AOC). This will allow the parents to make a decision whether to continue with the pregnancy.
- It is advisable to offer genetic counselling to parents of fetuses or infants with HPE or AOC.

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