HOLOPROSENCEPHALY AND CHROMOSOMAL ANOMALIES

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ABSTRACT

Holoprosencephaly is a rare cerebral malformation resulting from failure or incomplete cleavage of the forebrain. The sonographic diagnosis consists of monoventricle, fused thalami and absent cavum septum pellucidi. Chromosomal anomalies, diabetes mellitus, alcohol, autosomal recessive inheritance and toxins have been implicated. We describe seven cases of holoprosencephaly diagnosed in the antenatal and postnatal periods. The chromosomal anomalies included trisomy 13, triploidy, trisomy 13 with an unbalanced 13; 14 translocation and isochromosome of the long arm of 18. The clinicopathological findings and chromosomal anomalies are correlated.

Keywords: *holoprosencephaly, chromosome, anomaly, ultrasound*

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INTRODUCTION

Holoprosencephaly is a rare heterogenous group of cranial malformations resulting from failure or incomplete cleavage of the embryonic forebrain between the sixth and eighth menstrual weeks[1]. The brain shows undivided cerebral hemisphere with single ventricle, large coarse gyri, fused thalamus and absent corpus callosum. The disorder was first reported by Kundrat[2] in 1882. He coined the term arhinencephaly which included median dysplasia of the face, aplasia of the olfactory bulbs and tracts. Subsequent reports[3-5] established an association of holoprosencephaly with chromosomal defects, endocrine dysgenesis, facial and extracranial malformations. The frequency of holoprosencephaly has been reported between 1 in 5,200 to 1 in 16,000 livebirths[6,7]. We present seven cases of holoprosencephaly diagnosed in the antenatal and postnatal periods and will correlate the chromosomal, pathological findings and management.

MATERIALS AND METHODS

Between February 1993 and June 1994, seven cases of holoprosencephaly were diagnosed at Kandang Kerbau Hospital, Singapore. Six cases were diagnosed antenatally by ultrasound scans and one in the postnatal period. All except one antenatal fetus had karyotyping. The cases were discussed at the birth defect clinic and mid-trimester termination of pregnancy was performed in four out of six antenatal patients.

In this study, we discuss the embryology, chromosomal anomalies, prenatal diagnosis, associated facial and extracranial malformation, maternal characteristics, and review the perinatal management and outcome of this rare disorder.

Table I summarises the maternal age, gestation, fetal anomalies, karyotypes and outcome of the pregnancy.

Case 1

A 31-year-old Chinese gravida 3 para 1 booked at 21 weeks gestation for antenatal care. Routine ultrasound scan revealed holoprosencephaly, central facial cleft and ventricular septal defect. Amniocentesis showed a mosaic pattern of monosomy X in 16 cells and triploidy 68XX in 82 cells. The pregnancy was terminated with intravenous prostaglandins at 23 weeks gestation. Postmortem examination of a 425 gm female fetus showed an enlarged head with rudimentary nose, large central cleft lip and cleft palate. The brain was globular with a single ventricular cavity covered by thin membrane of meninges posteriorly. The basal ganglia, thalami and colliculi were exposed in the floor of the ventricular cavity. The cerebellum and brain stem were normal.

Case 2

A 21-year-old Malay gravida 3 para 2 booked at 23 weeks gestation. Ultrasound scan showed a single fetus with holoprosencephaly, hypotelorism, cleft lip, omphalocele and polydactyly of toes. Amniocentesis showed a male fetus with trisomy 13 and an unbalanced 13: 14 translocation [46XY, -14, t(13q 14q)]. The patient refused mid-trimester termination of the pregnancy. Her oral glucose tolerance test was normal. At 39 weeks gestation the fetus died in-utero. She went into spontaneous labour and delivered a macerated stillbirth. The parents refused post-mortem examination. External examination confirmed the ultrasound scan findings.

Case 3

A 27-year-old Chinese primigravida booked at 7 weeks of amenorrhoea. At 21 weeks gestation ultrasound scan revealed holoprosencephaly, hypotelorism and short femurs. Cordocentesis showed a normal 46XX karyotype. The pregnancy was terminated at 23 weeks with vaginal prostaglandins. Postmortem examination showed a 245 gm female fetus with typical dysmorphic features of hypotelorism, tubular nose with

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Table I – Summary of holoprosencephaly cases

Case No	Maternal age	Gestation week	Cranial anomaly	Extra-cranial and facial anomalies	Karyotype	Outcome
1	31	21	yes	VSD, cleft palate and lip	68 XX triploidy	MTPT*
2	21	23	yes	omphalocele, cleft lip, polydactyly	46XY, -14, +t(13q, 14q)	IUD* at 39 weeks
3	27	21	yes	single nostril	46XX	MTPT
4	32	28	yes	uni-lobed right lung, both testes, uterus and cervix	46 XY, i(18q)	Preterm delivery
5	34	16	yes	facial cleft, single nostril	46XX	Preterm delivery
6	33	19	yes	dysplastic kidneys	refused	MTPT
7	27	21	yes	cyclops, proboscis, absent left ear, ASD, VSD, megaureters, hypoplastic leg, single umbilical artery	47 XY, +13	MTPT

* Abbreviations: ASD - atrial septal defect, IUD - intrauterine death, MTPT - mid-trimester pregnancy termination, VSD - ventricular septal defect.

single nostril. The anterior cranial fossa was shallow with absent cribiform plate. The brain was univentricular with absent gyri and olfactory nerves.

Case 4

A 32-year-old obese Indian gravida 3 para 2 with parental diabetes booked at 11 weeks gestation. Early ultrasound scan did not reveal any anomaly. At 28 weeks she presented with preterm labour and premature rupture of membranes. Dexamethasone was given to enhance fetal lung maturity. Three days later she delivered a male fetus of 725 gm. The newborn was dysmorphic and died one hour after birth. Postmortem examination revealed alobar holoprosencephaly with single ventricle, uni-lobed right lung, bisexual organs with testes, uterus and cervix. Chromosome culture of fetal blood showed male karyotype with an isochromosome of the long arm of 18 [46 XY, i(18q)].

Case 5

A 34-year-old obese Indian primigravida with insulin dependent diabetes mellitus was admitted at 8 weeks gestation for diabetic control. The glycosylated haemoglobin was 9.4%. The diabetic control was unsatisfactory due to poor compliance. At 16 weeks gestation, ultrasound scan showed brachycephaly, hypotelorism, single cerebral ventricle, fused thalamus, and holoprosencephaly. The patient refused amniocentesis. At 22 weeks she went into spontaneous premature rupture of membranes and aborted a 570 gm female fetus. Post-mortem examination confirmed alobar holoprosencephaly, midline facial cleft, single nostril, hypotelorism, prominent epicanthic folds and protruding eyeballs. The fetal blood chromosomal karyotype showed 46XX.

Case 6

A 33-year-old Malay diabetic gravida 2 para 0 with previous macerated stillbirth was admitted at seven weeks gestation for diabetic control. Ultrasound scan at 19 weeks gestation showed severe oligohydramnios, univentricle, holoprosencephaly and dysplastic kidneys. She refused amniocentesis but accepted termination of the pregnancy. Following intravenous sulprostone prostaglandin infusion, she aborted a 285 gm dysmorphic male fetus. She refused post-mortem examination.

Case 7

A 27-year-old Chinese primigravida booked at 9 weeks amenorrhoea for antenatal care. At 21 weeks, ultrasound scan revealed cyclops, holoprosencephaly, proboscis, megaureters, thick walled distended bladder and a single umbilical artery. The pregnancy was terminated at 22 weeks with vaginal prostaglandins. Postmortem examination showed a 400 gm male fetus with multiple congenital abnormalities of the brain, heart and renal tracts. These included alobar holoprosencephaly, cyclops, absent left ear, hypoplastic right leg, right foot and hexadactyly of both hands and left foot. The heart revealed a secundum atrial septal defect and a doubly committed juxtaarterial ventricular septal defect. Both renal pelvis were dilated with hypertrophied left ureter and bladder. The post-abortal karyotype revealed trisomy 13 (46XY, + 13).

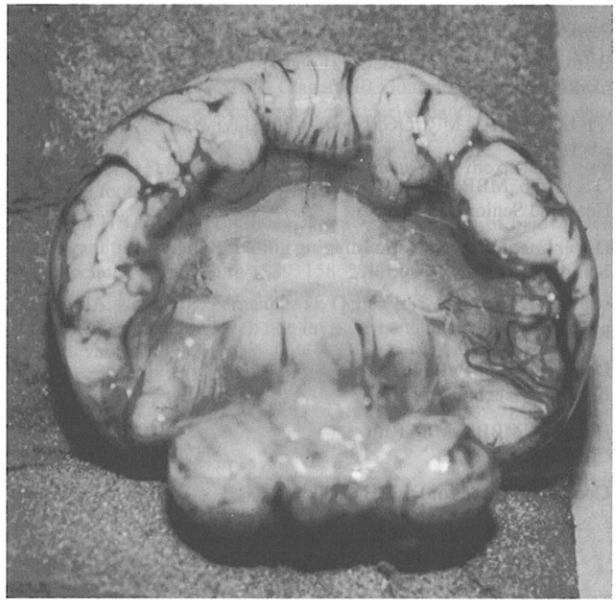
DISCUSSION

Embryologically, the neural tube differentiates into the brain and spinal cord. By the end of the fourth fetal week, the cephalic end of the neural tube has three primary vesicles which differentiate into the forebrain prosencephalon, midbrain mesencephalon and hindbrain rhombencephalon. The prosencephalon differentiates into telencephalon and diencephalon.

On day 32 of fetal life, a pair of bubble-like outgrowth of telencephalic vesicles forms the cerebral hemispheres and lateral ventricles. The diencephalon develops into the thalamus, hypothalamus and third ventricle. Failure of normal diverticularization and rotation of the prosencephalon into two normal cerebral hemispheres will result in holoprosencephaly.

DeMeyer[8] classified holoprosencephaly into three types: mild lobar, semilobar and the severe alobar types. The alobar holoprosencephaly has indistinct interhemispheric fissure, single ventricle, fused thalamus, absent corpus callosum, falx cerebri, optic tracts and olfactory bulbs[9,10]. The semilobar holoprosencephaly has rudimentary hemispheric lobes, incomplete interhemispheric fissure, rudimentary occipital horns, falx cerebri, incomplete fusion of the thalami, single distended

Fig 1 -- Alobar holoprosencephaly with single ventricle



ventricle with roofed membrane and absent cavum septum pellucidum. The mild lobar holoprosencephaly has normal separation of the ventricles and thalami but absent septi pellucidi and olfactory tracts.

The antenatal diagnosis of holoprosencephaly is based on the absence of midline echo, single dilated midline ventricle replacing the two lateral ventricles, and fused thalami. The falx, corpus callosum and cavum septi pellucidi are usually absent. Additional demonstration of facial abnormalities of hypotelorism, cyclopia, cebocephaly, midline clefts make a more confident diagnosis. Sonographically, holoprosencephaly may be confused with other malformations; hydrocephalus, Dandy-Walker malformation, arachnoid cyst, hydranencephaly and porencephaly[5,10].

Holoprosencephaly is commonly associated with facial malformations. The degree of facial malformation often predicts the severity of the cranial anomalies. The mild degree has minimal midface anomalies, cleft lips, cleft palate, hypotelorism, and trigonocephaly. The severe malformations include cyclopia, proboscis, cebocephaly with single nostril.

Extracranial malformations and multiple anomaly syndromes are frequently found in both alobar and semilobar holoprosencephaly. Renal cysts, omphalocele, cardiovascular malformations, clubfoot, myelomeningocele, intestinal abnormalities, Meckel-Gruber syndrome, Kallmann's syndrome, campmelic dysplasia, Hall-Pallister and Vasadi syndromes have been identified[10].

The aetiology of holoprosencephaly is heterogenous. In most cases it occurs sporadically but there is strong association with chromosomal anomalies[3,11]. Autosomal recessive inheritance[12], diabetes mellitus[13,14], drugs[15], ethanol[16], retinoids[17] and cytomegalovirus[18] have been implicated.

The frequency of chromosome abnormalities in holoprosencephaly varies from 11% to 35% Nicolaides[11] reported 26% fetuses (15 of 58) with holoprosencephaly had abnormal karyotype. The commonest chromosomal anomaly is trisomy 13. Others include 13q-, trisomy 18, 18p-, 21q- and triploidy. In our study, two fetuses had normal 46XX chromosomes but four had chromosomal anomalies including trisomy 13, triploidy (68XX), trisomy 13 with an unbalanced 13:14 translocation [46XY, -14, +(13q 14q)] and isochromosome of the long arm of 18 [46XY, i(18q)].

In holoprosencephaly, abnormal chromosomes are associated with multisystem malformations. Berry[3] analysed blood karyotyping in 38 fetuses with holoprosencephaly and reported 52% chromosomal defects in 11 of 21 holoprosencephalic fetuses with extrafacial defects but in none with isolated holoprosencephaly or facial defects only. In our study we have the same observation. None of the two holoprosencephalic fetuses with normal karyotype has extrafacial abnormality but all four fetuses with chromosomal abnormality had extracranial malformations which include cyclops, proboscis, omphalocele, ventricular septal defect, atrial septal defect, megaureters, bisexual organs and polydactyly.

In Case 2, the fetus had alobar holoprosencephaly, hypotelorism, omphalocele, polydactyly and trisomy 13 with unbalanced 13:14 translocation. Though it does not fall into the new "pseudo-trisomy 13 syndrome" as described by Cohen and Gorlin[19] of normal chromosomes with holoprosencephaly, severe facial anomalies, postaxial polydactyly and other congenital defects, the prognosis is equally grave.

Holoprosencephaly, like neural tube, cardiac and caudal defects, is specifically increased in fetuses of diabetic mothers. Barr[13] reported that holoprosencephaly is at least 200 times more frequent in insulin dependent diabetics than the general population. The probable explanation is that these defects share a critical period of development in the first few weeks of life.

In our study, two patients had insulin dependent diabetes and one of them had previous history of macerated stillbirth. There was no family history of congenital malformations, consanguinity, alcoholism and drug abuse in all the patients.

Hence, an analysis of family history of diabetes mellitus, oral glucose tolerance test, karyotype of the affected fetus are useful in establishing an aetiology of holoprosencephaly. The risk of recurrence in cases of primary trisomy is less than 1%, while in the presence of a parental balanced translocation the risk is 12%-30%[3].

In most cases, holoprosencephaly is incompatible with life. However, babies with lobar holoprosencephaly can survive with a variable degree of handicap. In our series, all seven cases had alobar holoprosencephaly with bad prognosis. Facial anomalies were present in four fetuses with cleft lip, cleft palate, rudimentary nose, single nostril and protruding eyeballs. Five fetuses had extracranial anomalies with ventricular septal defect, omphalocele, polydactyly and dysplastic kidneys. In Case 4, the unusual presentation of both male and female organs was seen in the fetus with isochromosome of the long arm of 18.

In our institution, all abnormal antenatal and postnatal cases including holoprosencephaly fetuses were discussed in the birth defect clinic which comprises obstetricians, geneticist, paediatricians, pathologists, pediatric surgeons, social workers and cytogenetic staff. All patients are counselled and karyotyping with either amniocentesis or cordocentesis is done. The management and prognosis are discussed with the parents. In our series, four antenatal patients had termination of pregnancy owing to poor prognosis, two developed premature labour with subsequent perinatal death.

In conclusion, holoprosencephaly carries a poor prognosis. Detailed ultrasound screening, genetic karyotyping, counselling and termination of abnormal fetuses may reduce the risk of stillbirth and perinatal mortality.

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