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Alobar holoprosencephaly: a case report



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ABSTRACT

Introduction: Holoprosencephaly (HPE) is a rare congenital malformation of the brain; the incidence rate was 0.49-1.2 cases per 10,000-20,000 term births. HPE occurs due to failure of the prosencephalon division at the stage of brain development during the 4-5 weeks of pregnancy. Alobar HPE is one of the most severe types compared to other types. Most of the fetuses affected by this anomaly will die, and those born alive generally cannot survive for more than a year. This study presented a rare case of a baby with alobar HPE.

Case report: A 33-year-old woman referred from Karang asem hospital Bali, G3P0020, 23 weeks gestation, has a poor obstetric history. The ultrasound examination results show no falx cerebri, even cerebellum and hypoechoic picture of the cerebrum. Ultrasound of the face was found a flat nose and hypotelorism. Termination at 28 weeks gestation, a baby boy was born 1000 g with the Apgar score 1-1. Multiple congenital abnormalities were found: flat nose, labiopalatoschizis, polydactyly manus dextra and omphalocele.

Conclusion: Alobar HPE is a very rare congenital anomaly. The cause of the disease has not been fully explained. Current therapy is just supportive and has not been able to resolve the source of the problem. Alobar HPE disease has a poor prognosis.

Keywords: holoprosencephaly, alobar, congenital anomaly, fetus

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INTRODUCTION

Holoprosencephaly (HPE) occurs due to failure of the prosencephalon's midline division, so it becomes an anomaly of fetal brain development. The prosencephalon is supposed to form the cerebral hemispheres, thalami and basal ganglia. Failure of division in the prosencephalon usually occurs in the 4-5th week of gestation.^{1,2} Holoprosencephaly is a rare, severe malformation with facial dysmorphism and neurologic disturbances. Holoprosencephaly is reported to occur in 0.49 to 1.2 cases per 10,000-20,000 births at term. In the United States, the prevalence of HPE is reported to be higher in Latinos, African-Americans and Pakistanis.^{2,3}

Holoprosencephaly is thought to occur due to genetic, environmental, and mechanical factors. Genetic factors include aneuploidy chromosomal disorders, autosomal recessive syndrome, structural abnormalities to a history of diabetes

in the mother.⁴ Holoprosencephaly is divided into four types: alobar HPE, semi-lobar HPE, lobar HPE, and Middle Interhemispheric Fusion (MIH). Each type of holoprosencephaly is distinguished based on the severity of hemisphere division and the presence or absence of interhemispheric fissures; the classification of HPE types also serves as a determinant of prognosis in patients. Alobar HPE is the worst case among other HPE types. In alobar HPE, there is only a single ventricle, no interhemispheric fissures and the corpus callosum are found. In the semi-lobar type of HPE, there is a slight separation in the anterior hemisphere and an interhemispheric fissure in the posterior. Lobar HPE is the mildest type of HPE, with interhemispheric fissures in the anterior and posterior parts of the brain. MIH type occurs when there is a failure to separate the posterior parts of the frontal and parietal lobes, there is no corpus callosum body, but there is a gau and splenium from the corpus callosum.^{5,6}

Fetuses affected by alobar HPE will usually experience hypotelorism, cyclopia, nasal structure disorders to the absence of nasal bone formation, cleft lip, no incisors and midface hypoplasia. The imaging modalities of choice that we can use to assess HPE are transabdominal ultrasonography (USG), transvaginal USG, and magnetic resonance imaging (MRI).^{4,5} This study presented a rare case of a baby with alobar HPE.

CASE PRESENTATION

A 33-year-old woman came to the Sanglah Hospital, Denpasar, Bali; the patient was referred from the Karangasem Hospital with a diagnosis of G3P0020 23 weeks single alive, had a poor obstetric history with suspicion of ventriculomegaly. In the history taking, there was no abdominal pain, no contractions, no discharge from the birth canal, and the mother felt good fetal movement, no fever, and no other comorbidities. Abnormalities on USG

were first discovered on December 23rd, 2018. The patient did not remember the first day of the last menstruation. The patient has no history of allergies, no previous medical history, unknown history of tetanus toxoid vaccine, and a history of laparotomy surgery in 2005 at Lombok Hospital. Patients do antenatal care at the obstetrician more than three times. There are no other complaints in the current pregnancy. The patient's menstrual history, menarche at the age of 14 years, a blood volume of 30-40 ml, regular 28-day menstrual cycle, 5-7 days of menstruation, and the patient had no complaints during menstruation. History of previous pregnancy and childbirth in 2005, a pregnant patient with a diagnosis of disturbed ectopic pregnancy was terminated by laparotomy. In 2006 the patient was pregnant, but at eight weeks of gestation, an abortion occurred. There is no family history of the patient's condition.

On physical examination, the patient's general condition was good, Glasgow coma scale (GCS) E4V5M6, maternal blood pressure 100/70 mmHg, pulse 84 times per minute, respiration 20 times per minute, body temperature 36.9°C, pain scale 0. Obstetric status, on the abdomen, uterine fundal height is two fingers above the navel, there is no his or contraction, positive fetal heart rate in 140 times per minute, the intravaginal examination is not performed. On ultrasound examination, biparietal diameter (BPD): 5.72 cm ~ 20W5D, head circumference (HC): 20.36 cm ~ 22W1D, abdominal circumference (AC): 17.11 cm ~ 22W1D, femur length (FL): 3.83 cm ~ 22W2D. The placenta was in the posterior corpus fundus grade II, single deepest pocket (SDP): 2.85 cm,

found a flat nose, hypotelorism, and alobar type HPE (Figure 1, 2, and 3). The patient was diagnosed with G3P0020 at 23 weeks five days of single life with fetal congenital anomaly alobar type HPE. Management is planning to do amniocentesis. The results of the amniocentesis are not finished from the Prodia laboratory.

At 28 weeks of gestation, the patient came to Karangasem Hospital and was terminated with misoprostol with a diagnosis of G3P0020, gestational age of 28 weeks two days, single life, poor obstetric history, suspected intrauterine growth restriction (IUGR), congenital anomaly

of alobar HPE, with estimated fetal weight 984 grams, pelvic score (PS) 1. At 19.00, a baby boy was born with a weight of 1000 grams, head circumference of 26 cm, and Apgar score of 1-1. The baby was born with multiple congenital abnormalities, namely labiopalatoschisis, polydactyly manus dextra, and omphalocele (Figure 4 and 5).

DISCUSSION

A 33-year-old woman came for antenatal care. At the time of ultrasound examination, abnormalities were found with suspicion of ventriculomegaly, and

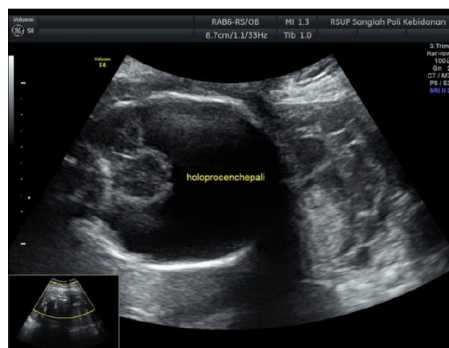


Figure 1. Ultrasound of the patient's holoprosencephaly



Figure 2. Ultrasound of flat-nose

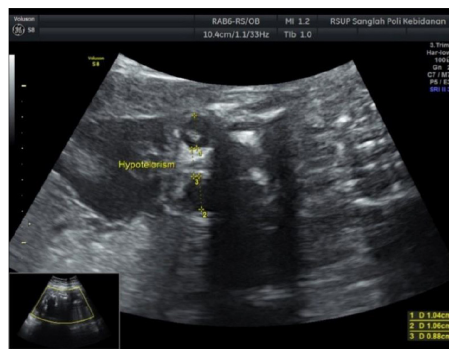


Figure 3. Ultrasound of hypotelorism

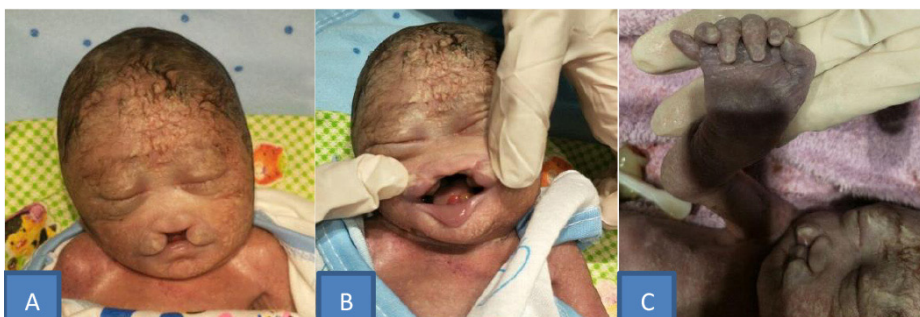


Figure 4. Photos of the baby being born. Figure A and B show the baby's labiopalatoschisis. Figure C shows the right manus polydactyly.



Figure 5. Photo of the baby with omphalocele

Table 1. Genes suspected of being associated with HPE.^{3,10}

Gene	Chromosomal Locus	Prevalence in HPE patients and genetic mutations	
		There is a family history	Simplex case
SHH	7q36	30%-40%	<5%
ZIC2	13q32	5%	2%
SIX3	2p21	1,3%	seldom
TGIF1	18p11.3	1,3%	seldom
GLI2	2q14	Unknown	Unknown
PTCH1	9q22.3	Unknown	Unknown
DISP1	1q42	seldom	seldom
FGF8	10q24	seldom	seldom
FOXH1	8q24.3	seldom	seldom
NODAL	10q22.1	seldom	seldom
TDGF1 (CRIPTO)	3p23-p21	seldom	seldom
GAS1	9q21.33	seldom	seldom
DLL1	6q27	seldom	seldom
CDON	11q24.2	seldom	seldom

the patient was referred to the fetomaternal poly at Sanglah Hospital Denpasar, Bali. At the outpatient clinic, an ultrasound examination was performed. The examination results revealed an anomaly, namely holoprosencephaly of the alobar type. The patient is advised to perform an amniocentesis. The amniocentesis examination was carried out on January 10th, 2018, at the Prodia clinical laboratory. At 28 weeks of gestation, the patient was terminated at Karangasem Hospital with indications of hydramnios. There is a gap in this case; patients with cases of congenital abnormalities like this tend to have complications to the mother and fetus to be treated in a tertiary hospital or a type A referral hospital. The treatment given to the patient must be in accordance with the availability of medical equipment and personnel—specialists who are complete and competent to help mothers and fetuses with congenital abnormalities like this. Fetuses with a gestational age of 28 weeks after birth require intensive treatment and must be treated in a complete Neonatal Intensive Care Unit (NICU) to support the continuation of neonate life.⁷

The incidence of holoprosencephaly is very rare in the world. The first time holoprosencephaly was reported by Kurtz et al. in 1980, subsequently developed into several studies and several case reports that explain the findings through ultrasound. At 4-5 weeks of gestation, the prosencephalon normally divides, but in

the case of the HPE, there is a failure of division in the left and right hemispheres.⁶ Since the first trimester has occurred, the formation of most of the brain neurons and most of the formation of the structure of the central nervous system, then in the second trimester will continue to form and develop these neurons and central nervous structures. A disturbance of formation and development in the first or second trimester will cause severe structural abnormalities in the fetus. Furthermore, if there is a disturbance in the formation and development of the brain in the third trimester, microstructural and functional damage will occur because, at this time, the final maturation of the central nervous system in the fetus occurs before birth. Brain development will go through a period of the brain growth spurt; in this period, the brain will develop very quickly. The period of the brain growth spurt occurs for the first time, starting when the mother enters the third trimester of pregnancy.^{8,9}

Several previous studies have explained that the cause of holoprosencephaly has a relationship with genetic and environmental factors. Genetic factors are closely related to chromosomal abnormalities such as trisomy 18 or Edward syndrome, trisomy 13 or Patau syndrome, trisomy 17, trisomy 15, and triploidy. Patients with HPE have chromosomal abnormalities of about 25-50%. The abnormality is non-specific

and can be numerical or structural. All of the above chromosomal abnormalities have been reported to be associated with the cause of HPE.¹⁰ Environmental factors that can influence the occurrence of holoprosencephaly are mothers with a history of diabetes mellitus. As many as 1% of mothers with diabetes mellitus will give birth to babies with HPE. Other factors are still in the research stage, but in experimental animal studies, it is reported that consuming alcoholic beverages and retinoic acid can cause HPE.^{6,11}

Patients with holoprosencephaly are usually the first to be identified during antenatal care, and an ultrasound examination is performed. On ultrasonographic examination, abnormalities and types of the severity of the failure of this prosencephalon division can be found. In addition to the ultrasound, we can also use MRI. On ultrasound examination, we can also find congenital abnormalities on the face, such as cyclopia, hypotelorism, and a flat nose. However, in infants with mild facial or brain abnormalities, it is usually difficult to diagnose and will be known if the baby is one year old with developmental disorders or failure to grow.¹² Mothers with a history of giving birth to children with HPE or in the family have a history of disease caused by gene mutations, the examination that can be done is molecular genetic testing. This examination is carried out by amniocentesis, taking some fetal cells to examine fetal DNA to see if there are chromosomal abnormalities at 15-18 weeks of pregnancy; it can also use chorionic villus sampling (CVS) at 10-12 weeks of gestation.¹³

Fetuses with holoprosencephaly will experience facial disturbances or facial dysmorphic occurrence. Disorders of the face in the patient found labiopalatoschisis and a flat nose. Babies born with this disorder will undergo facial repair.¹⁴ Surgery will usually be done repeatedly according to the severity. Repair of the lips will usually be done on the patient at the age of 3 months and will take a long time to return to normal. Post-surgical care is the most important thing to pay attention to. Later, the baby will be fitted with an arm restraint device to prevent damage to the area of the surgery site on the lips due

to the baby's arm accidentally damaging it.¹⁵ This study's limitation is that we only did some initial and supportive care to the patient and her baby but did not follow up until the end.

CONCLUSIONS

Holoprosencephaly is a rare congenital anomaly. Alobar holoprosencephaly is the most severe case among other types; the prognosis of this type is poor and requires special care for babies born. The cause of this disease is suspected to be related to genetic and environmental factors, but until now, the cause has not been fully explained. Therapy given to the mother and fetus with a diagnosis of holoprosencephaly is currently still supportive and has not been able to resolve the source of the problem. Infants who have been born with congenital abnormalities of brain development and facial dysmorphic need intensive treatment and must be carried out in a type A hospital that has complete facilities to support the baby's life and for further management.

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PATIENT'S CONSENT

The patient did give informed consent regarding the publication of this case.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest regarding this study.

AUTHOR CONTRIBUTION

All of the authors contributed equally to this study.

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