Holoprosencephaly, a disorder resulting from failure of cleavage or incomplete differentiation of the forebrain structures at various levels or to various degrees, is related to hereditary factors, chromosomal anomalies, cytogenetic abnormalities, and environmental teratogenic factors. We report on 2 cases of alobar holoprosencephaly, with similar physical findings, including microcephaly, microphthalmia, ceboccephalus, choanal atresia, pseudo cleft palate, distended abdomen, and acrocyanosis. The brain echogram of these 2 patients demonstrated fused thalami and a single large U-shaped ventricular cavity. Chromosome studies of these 2 patients were normal. The findings of the autopsies confirmed the clinical presentations. One of our cases had a clinical picture similar to that of holoprosencephaly-polydactyly syndrome. The other had the rare anatomical finding of a polylobuated spleen. Because of the poor prognosis of alobar holoprosencephaly, early prenatal diagnosis is recommended. (Chang Gung Med J 2003;26:700-6)

Key words: alobar holoprosencephaly, polydactyly, polysplenia.
CASE REPORT

Case 1

This was the second pregnancy of non-consanguineous parents, aged 33 and 35 years, respectively.

The first pregnancy of the mother had ended with a spontaneous abortion. There was a history of neither hereditary disease nor chromosome disorders in either family. The mother had received no regular

Fig. 1 Case 1. (A) Anterior view of the face; (B) brain sonogram; (C) single large ventricle without septation; and (D) polylobulated spleen.
prenatal checkups, including ultrasound examination, during the entire course of the pregnancy; hence, no diagnosis was made during the prenatal stage. In the 38th week of gestational age, a female baby weighing 3200 g was born via cesarean section due to premature rupture of the membrane for 8 hours. General cyanosis and delayed initial crying occurred immediately after delivery. The Apgar scores were 5 at 1 min and 7 at 5 min. She was immediately admitted to the neonatal intensive care unit. Physical examinations showed lethargy, microcephaly (less than the 3rd percentile), short stature (less than the 3rd percentile), microphthalmia, hypotelorism, cebocephalus, choanal atresia, pseudo cleft palate, a moderately distended abdomen, and acrocyanosis. The newborn died on the third day of life. A brain echogram performed on the first day of admission showed a fused thalamus and a single large U-shaped ventricular cavity. The chromosomal analysis showed a 46,XX, normal karyotype.

An autopsy was performed with the parents’ consent. The abnormal findings of the autopsy included: (1) a single large ventricle with an opening to the posterior part of the brain, (2) the absence of olfactory and optic nerves, (3) dysgenesis of the hypopituitary, thyroid, and adrenal glands, (4) choanal atresia, (5) no lobulation of the left lung, and (6) polylobulation of the spleen.

Case 2

This female baby was born to 34- and 31-year-old, non-consanguineous parents who had suffered

Fig. 2 Case 2. (A) Anterior view of the face; (B) brain sonogram; (C) preaxillary polydactyly; and (D) single large ventricle without septation.
from infertility for 3 years. The primigravida was transferred to our obstetric department for confirmation of hydrocephalus which was suspected during the last month of pregnancy by local medical clinics. Fetal ultrasonography at 37 weeks of gestation revealed oligohydramnios, microcephaly, a single large ventricle, a fused thalamus, and hypotelorism. A tentative prenatal diagnosis of alobar holoprosencephaly was made. A child weighing 2900 g was born at 38 weeks of gestation by cesarean section due to breech presentation. A delay of initial crying was found after delivery. The Apgar scores were 4 at 1 min and 6 at 5 min. There were similar abnormal physical findings as those of case 1, including microcephaly, microphthalmia, hypotelorism, cleft palate, a pseudo cleft palate, and choanal atresia; preaxial polydactyly of the left hand was an additional finding. The results of a postnatal brain echogram were the same as those of the prenatal stage. She died at 30 hours of age. The karyotype of the patient was 46,XX. The abnormal findings by autopsy included: (1) a single large ventricle with an opening to the posterior part of the brain and a fused thalamus, (2) the absence of olfactory and optic nerves, (3) dysgenesis of the hypopituitary, thyroid, and adrenal glands, (4) choanal atresia, and (5) polydactyly.

**DISCUSSION**

During the third week of embryonic life, the prechordal mesoderm migrates into the area prior to the notochord and affects midline facial development; hence, before 4 weeks of embryonic age, the varying degrees of loss or disruption in the development of prechoral mesoderm cause abnormal forebrain development and midfacial defects. Holoprosencephaly, the most common structural anomaly of the developing forebrain and midface in humans, is a disorder in which the cephalic neural tube fails to develop and does not divide into right and left lobes. Holoprosencephalon is the term used to describe a single, unpaired forebrain.

The epidemiology of holoprosencephaly indicates interactions with both genetic and environmental factors, including chromosomal anomalies, gene rearrangements, mendelian mutations, and teratogens, and it can usually be determined.

Although it is extremely heterogeneous, there may be a common final pathway for the abnormal development of the forebrain and face. The majority of holoprosencephaly cases are sporadic; cases of familial holoprosencephaly are reported to be autosomal dominant, autosomal recessive, or X-linked in inheritance. Nearly 50% of all holoprosencephaly cases have cytogenetic abnormalities, and approximately 18%-25% of patients of holoprosencephaly have a documented monogenic syndrome. To the present, there are at least 12 known loci which may contain genes critical for normal brain development on 11 chromosomes. Trisomy 13 is the most commonly identified cause; others include trisomy 18, HPE1(21q22.3), HPE2(2p21.SIX3), HPE3(7q36, SHH,SonicHedgehog), HPE4(18p11.3,TGIF), HPE5(13q32,ZIC2), HPE6(3p24-pter), HPE7 (13q12-q14), HPE8(14q13), HPE9(20p13), HPE10 (1q42-qter), HPE11(5p), HPE12(6q26-qter), t(7;13)(q21.2;q33), 3q22 deletion,13q33, q34 or 35- qter deletion, 7q36-qter deletion, and 14q22 deletion,del(14)(q11.1q13). Environmental teratogens reported to induce holoprosencephaly include maternal diabetics (with a reported 200-fold increase in the incidence of holoprosencephaly in infants of diabetic mothers over infants of non-diabetic mothers), steroid alkaloids, thanol, and retinoic acid. Syndromatic associations include Martin syndrome, Steinfeld syndrome, CHARGE association, Meckel-Gruber syndrome, Kallmann syndrome, Hall-Pallister syndrome, Vaisidi syndrome, Smith-Lemli-Opitz syndrome, holoprosencephaly-polydactyly syndrome, and Rubenstein-Taybi syndrome. Associated abnormalities include microcephaly,
hydrocephalus, agenesis of the corpus callosum, posterior fossa abnormality, cerebellar vermis aplasia, myelomeningocele, absence of an olfactory bulb, a cleft lip/palate, adrenal hypoplasia, renal dysplasia, renal cysts, omphalocele, cardiovascular malformations, intestinal abnormalities, club foot, sirenomelia,(13) spina bifida, and endocrinopathies (pituitary gland dysplasia, growth hormone deficiency, and diabetes insipidus). (14) Knowing the etiologies of holoprosencephaly is important for establishing the risk of recurrence.

One of our cases with a normal karyotype, who possessed polydactyly, and adrenal and thyroid gland dysgenesis, is compatible with the clinical picture of holoprosencephaly-polydactyly syndrome, a more-neutral term recommended by Verloes et al. (12) to substitute for the previous term of pseudotrisomy 13 syndrome suggested by Hewitt et al. (15) The characteristics of the polydactyly in our patient was of the preaxial type, in comparison to the postaxial polydactyly in all reported cases of holoprosencephaly-polydactyly syndrome. Most cases of holoprosencephaly-polydactyly syndrome are sporadic, but autosomal recessive and autosomal dominant modes of inheritance have also been reported. The hypothesis is that a chromosomal rearrangement or duplication occurs between 13q31 and 13q34. In 1991, Raoul suggested the use of the descriptive name of autosomal recessive holoprosencephaly, heart defect, and postaxial polydactyly syndrome. (16) In 1993, Lurie and Wulfsberg suggested the use of an eponymic name, such as the Cohen-Gorlin syndrome, because they found that neither holoprosencephaly nor polydactyly was an obligatory manifestation of this disease entity. (17) One of our patients had polysplenia which is a rare finding in holoprosencephaly cases.

The phenotypic expression of holoprosencephaly varies widely. "The face predicts the brain" as recommended by DeMyer et al. in 1963 (10) is correct in about 70%-80% of cases, but not in all children with holoprosencephaly. The craniofacial anomalies include cyclopia (a single eye or partially divided eyes in a single orbit with a proboscis above the eye), ethmocephaly (severe hypotelorism and a proboscis between the eyes), cebocephaly (hypotelorism, a single nostril, and a blind-ended nose), premaxillary agenesis, arhinencephalia (the absence of olfactory bulbs and tracts), agenesis of the corpus callosum. Facial-only phenotypes include midface hypoplasia, hypotelorism, coloboma, microphthalmia, unilateral or bilateral clefts, solitary central incisor and/or pyriform aperture stenosis, hypotelorism, the absence of nasal bones or a flat nose, and the absence of the upper lip midline frenulum. Milder forms may be unrecognized if imaging studies of the brain are not arranged.

Patients with severe forms of holoprosencephaly usually die during the first year of life. (19) Both of our cases who were diagnosed to be of the alobar type expired within 3 days after birth. The less-severe forms, i.e., semilobar or lobar holoprosencephaly, may allow longer life spans if other associated abnormalities are not life threatening. But all survivors have the inability to smell, developmental delay, profound intellectual impairment, and seizures. (18) Other problems include (1) increased muscle tone to the point of spasticity, poor control of muscles, and contractures; (2) fluctuating behavior between calmness and irritability, with sudden changes in mood; (3) hoarse, barking, or a high-pitched voice; (4) difficulty with swallowing, choking spells and gagging during feedings, spitting up, frank vomiting, risk of aspiration, and constipation; (5) growth delays, (6) sleep disturbances; (7) periodic brain stem and/or hypothalamus dysfunction with irregular breathing, heart rhythm, and heart rate, and unstable temperature control; and (8) pituitary and/or thyroid gland dysfunction. (18) The cause of death is usually abnormal brain stem function, especially superimposed with infection, diabetes insipidus causing severe dehydration, or intractable seizures.

Early detection by sonography offers a better and earlier diagnostic procedure than amniocentesis. The earliest gestational age at the time of diagnosis was 14 weeks. Because of the short life span and ominous outcome in all patients with alobar holoprosencephaly, genetic counseling and prenatal diagnosis by ultrasound (transabdominal or transvaginal scanning) are of great importance for early detection and allows earlier termination of the pregnancy. (19)

In summary, we report on 2 cases of alobar holoprosencephaly with the special findings of polysplenia in case 1 and preaxial polydactyly in case 2. The variety of clinical pictures and the complexity of genetics in holoprosencephaly require further investigations in clinical, radiological, pathological, genetic, embryological, and teratogenic fields.
REFERENCES

無分葉性全前腦症：二病例報告

張莉幸

全前腦症是由於前腦在分裂或分化過程中不同階段或不同程度的不完全發育所造成。本文提出二例報告，其類似的臨床表現為小頭、小眼、眼距過近、單一鼻孔、後鼻孔不通、假性頭裂、腹裂及四肢發紫，相同的超音波檢查發現為單一U型腦室和合而為一的丘腦，相同的病理解剖報告為單一腦室，後方有一開口、合而為一的丘腦，沒有嗅神經及視神經，腦下腺、甲狀腺及腎上腺皆發育不良。兩患者染色體檢查皆正常。其中病例一具有少見之多分葉型脾臟，病例二具有全前腦症－多指症候群之臨床特徵。因此症預後差，建議及早作產前診斷。(民國93年26:700-6)

關鍵字: 無分葉性全前腦症，多指症，多分葉型脾臟。