Cebocephaly, alobar holoprosencephaly, spina bifida, and sirenomelia in a stillbirth

Chih-Ping Chen, Shin-Lin Shih, Fen-Fen Liu, Sheau-Wen Jan

Abstract
Cebocephaly and sirenomelia are uncommon birth defects. Their association is extremely rare; however, the presence of spina bifida with both conditions is not unexpected. We report on a female stillbirth with cebocephaly, alobar holoprosencephaly, cleft palate, lumbar spina bifida, sirenomelia, a single umbilical artery, and a 46,XX karyotype, but without maternal diabetes mellitus. Our case adds to the examples of overlapping cephalic and caudal defects, possibly related to vulnerability of the midline developmental field or axial mesodermal dysplasia spectrum.
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Keywords: holoprosencephaly; cebocephaly; sirenomelia; spina bifida.

Holoprosencephaly (HPE), a severe form of cephalic defect with an incidence of 0.63 in 10 000 live births with normal chromosomes,²³ is characterised by an anomalous craniofacial complex that involves a series of forebrain and midface malformations of graded severity.²⁴ HPE is associated with teratogenic and genetic factors. Alcohol and maternal diabetes are known teratogenic factors. There is a 200-fold increase in the incidence of holoprosencephaly in infants of diabetic mothers over infants of non-diabetic mothers.²⁵ Animal models involving the ingestion of the plant *Veratrum californicum*, which contains steroidal alkaloids, can produce cyclopia in sheep embryos.²⁶ Cytogenetic abnormalities have been reported in 50% of all HPE patients and the specific chromosome aberrations include trisomy 13, trisomy 18, triploidy, del(13q), dup(13q), del(18p), del(7)(q36), dup(3)(p24-pter), del(2)(p21), and del(21)(q22.3).²⁵ At the Human Gene Mapping 11 Conference,²⁷ four putative HPE genes were designated: HPE on chromosome 21q22.3, HPE2 on 2p21, HPE3 on 7q36-qter, and HPE4 on 18pter-q11. Familial HPE with a normal karyotype has been described with autosomal dominant, recessive, and X linked

Department of
Obstetrics and
Gynaecology, Mackay
Memorial Hospital, 92,
Section 2, Chung-Shan
North Road, Taipei,
Taiwan, Republic of
China
C-P Chen

Department of
Radiology, Mackay
Memorial Hospital, 92,
Section 2, Chung-Shan
North Road, Taipei,
Taiwan, Republic of
China
S-L Shih

Department of
Medical Research,
Mackay Memorial
Hospital, 92, Section 2,
Chung-Shan North
Road, Taipei, Taiwan,
Republic of China
C-P Chen
F-F Liu
S-W Jan

Correspondence to:
Dr Chen.

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Sirenomelia and holoprosencephaly are well defined congenital malformations that usually occur independently. Sirenomelia, a severe form of caudal defect with an incidence of 1.5-4.2 per 100 000 births,¹ is characterised by complete or incomplete fusion of the lower extremities. Various skeletal and podalic presentations of sirenomelia have been described.² There is a 100-150 fold increase in the incidence of sirenomelia in monozygotic twins over that in singletons and dizygotic twins.¹ The absence of chromosomal abnormalities and familial inheritance has been noted in almost all cases of sirenomelia. Administration of retinoic acid³ and cyclophosphamide⁴ to pregnant mice and hamsters, and destroying the axial portion of the caudal mesoderm of chicken embryos,⁵ have been reported to produce limb defects including sirenomelia. About 2% of sirenomelia cases are associated with maternal diabetes mellitus.⁶ Common associated abnormalities include hemivertebrae, spina bifida, meningocele, deformed pelvis, a single umbilical artery, abnormal internal and external genitalia, urinary tract anomalies, imperforate anus, pulmonary hypoplasia, tracheo-oesophageal fistula, and cardiovascular malformation.¹ Central nervous system (CNS) anomalies (table 1) present in less than 10% of patients with sirenomelia.

Table 1 Summary of previously reported cases of CNS abnormalities associated with sirenomelia

References	CNS abnormalities associated with sirenomelia
7	Craniorachischisis totalis (case report)
8	Craniorachischisis totalis (case report)
9	Anencephaly (case report)
10	Meningomyelocele, hydrocephalus and Arnold-Chiari malformation (1/11)
11	Atelencephaly and cebocephaly (case report)
12	Hydrocephalus (2/3)
2	Hydrocephalus (2/77), hydrocephalus and meningocele (1/77), Arnold-Chiari malformation, absent corpus callosum, and lumbar meningocele (1/77)
13	Anencephaly and cervicothoracic meningocele (case report)
14	Hydrocephalus (1/11); spina bifida occulta (1/11); spina bifida with meningocele (1/11)
15	Myelomeningocele, hydrocephalus, and others* (5/54)
16	Anencephaly (case report)
17	Meningocele (case report)
18	Neural tube defects (7/98) (6 low spina bifida, 1 cervical spina bifida); hydrocephalus (2/98); cyclopia (1/98)
19	Craniorachischisis totalis (case report)
20	4/101*
6	Meningomyelocele (1/4)
21	Cervicothoracic spina bifida (case report)
22	Thoracolumbar meningocele and Arnold-Chiari malformation (case report)
Present case	Cebocephaly, alobar holoprosencephaly, and lumbar spina bifida (case report)

*Nature of CNS abnormalities not reported.

Figure 1 Photograph of the sirenomelia stillbirth showing cebocephaly with ocular hypotelorism and a single nostril. The lower limbs are fused from the pelvis to the ankles and angulated 180° posteriorly in relation to the trunk.

inheritance.^{28 29} HPE has also been associated with Martin syndrome, Steinfeld syndrome, CHARGE association, Meckel-Gruber syndrome, Kallmann syndrome, Hall-Pallister syndrome, and Vasadi syndrome.^{25 30} Common associated abnormalities include microcephaly, undivided thalamus, agenesis of the corpus callosum, arhinencephaly, renal cysts and dysplasia, omphalocele, cardiovascular malformations, club foot, myelomeningocele, and intestinal abnormalities.³¹

Figure 2 (Left) Anterior view of the lower limbs showing the popliteal fossae and heels pointing forwards. (Right) Posterior view of the lower limbs and the trunk shows lumbar spina bifida, and the knees and toes pointing backwards. No external genitalia or anus are visible.

The association of holoprosencephaly and sirenomelia is extremely rare. In 1986, Young *et al*¹¹ first reported a twin infant, born at 33 gestational weeks, with cebocephaly, atelencephaly, and sirenomelia. Subsequently, only one patient with cyclopia, holoprosencephaly, and sirenomelia has been observed.¹⁸ Here, we report an additional case of holoprosencephaly with sirenomelia. To our knowledge, the combination of cebocephaly, alobar holoprosencephaly, cleft palate, spina bifida, and sirenomelia has not been previously reported.

Case report

The proband was stillborn at 28 weeks' gestation with a weight of 1500 g and a length of 38 cm. She was the second child of a 25 year old woman. The parents are Chinese, non-consanguineous, and healthy. There was no family history of diabetes mellitus, twins, or congenital malformations. Maternal urine throughout the pregnancy did not contain glucose. The mother had one healthy 2 year old child. She denied any exposure to drugs for ovulation before conception, or alcohol, teratogenic medication, irradiation, or infectious diseases during this pregnancy. Her pregnancy with this child was uneventful except that oligohydramnios was noted during the second trimester. At 28 weeks' gestation, ultrasonography indicated intrauterine fetal death.

Physical examination of the stillbirth showed microcephaly, ocular hypotelorism, a single nostril, cebocephaly (fig 1), malformed, low set ears, and cleft palate. Detailed evaluation showed soft tissue fusion of the lower limbs from the pelvis to the ankles. The feet were normally formed and fused at the heels. The fused lower limbs were angulated 180° posteriorly in relation to the trunk (fig 1). Both knees and toes pointed backwards. There was imperforate anus, spina bifida over the lumbar area, and absence of external genitalia (fig 2). The umbilical cord contained only a single umbilical artery and an umbilical vein. Radiographs showed two femora, two tibiae, two fibulae, incomplete rotation of the legs leading to a medial position of the fibulae, thin ribs, hypoplastic vertebrae, dextroscoliosis of the thoracolumbar spine, sacral agenesis, and poorly formed acetabula. Necropsy showed alobar holoprosencephaly with a single ventricle and spina bifida occulta over the lumbar area. Data on the internal organs were not available because of severe calcification and autolysis of the tissue. A cytogenetic study was performed on Giemsa banded chromosomes from cultured chorionic villi cells and showed a normal 46,XX karyotype.

Discussion

Our case is a rare combination of type I sirenomelia¹ with symphys dipus, alobar holoprosencephaly, cebocephaly, and spina bifida, without the association of maternal diabetes mellitus, monozygotic twins, abnormal chromosomal complements, or familial inheritance.

In 1989, O'Rahilly and Müller³² and in 1992, Källén *et al*¹⁸ suggested that cyclopia and sirenornelia have a similar mode of formation and both may share similar aetiological and pathogenetic factors affecting the development of the axial mesoderm. In holoprosencephaly, deficiency of prechordal mesoderm occurs at or before 4 weeks of embryonic age. During the third week of embryonic life, the prechordal mesoderm migrates forwards into the area anterior to the notochord and evolves into midline facial development. The prechordal mesoderm plays a reciprocal induction role in the morphogenesis of the neur ectoderm, the forebrain. Deficiencies of prechordal mesoderm cause midfacial defects as well as incomplete forebrain development.³³⁻³⁴ Sirenornelia is believed to originate before 30 days of embryonic life and to occur through a failure in later-alisation secondary to a mesenchymal deficiency of the caudal eminence.³² The caudal eminence contributes to the formation of the notochord, vertebrae, lower limb buds, perineum, neural plate, neural cord, hindgut, and blood vessels. An extensive disturbance of the axial mesoderm can cause concomitant alteration of neural ectoderm, and consequently neural tube defects occur.¹⁹ Theories proposed for the pathogenesis of sirenornelia can be categorised into the vascular disruption hypothesis and the caudal embryo damage hypothesis.¹⁰⁻²²⁻³⁵ The most likely mechanisms are believed to be a deficiency of the caudal mesoderm as well as a decrease of haemoperfusion in the caudal region and lower extremities of the embryo.¹ In 1982, Opitz and Gilbert⁸ proposed the concept of midline developmental field. They suggested that in early embryogenesis the midline is a weakly buffered field. Difficulties in the early process of determination because of midline vulnerability may cause both duplication and deficiencies.³⁶ Holoprosencephaly, spina bifida, cleft palate, and sirenornelia in this case all belong to the midline anomalies. In 1981, Russel *et al*²⁷ suggested the term "axial mesodermal dysplasia" to describe a disturbance during early embryogenesis which affects the mesodermal cell migration during the primitive streak period. Combined anomalies in both the cranial and caudal regions have been suggested as examples of axial mesodermal dysplasia.¹⁹ Our case shows the combination of the most extreme anomalies of the cephalic and caudal regions of the embryo, cebocephaly and sirenornelia. It is related to deficiencies of or damage to both prechordal mesoderm and caudal mesoderm during early embryonic life and can be considered an example of axial mesodermal dysplasia.

The prevalence of cases with a combination of some form of holoprosencephaly with any degree of caudal dysgenesis has been estimated at about 7.9 per million livebirths³⁸ which is significantly higher than would be expected by chance. Morichon-Delvallez *et al*³⁹ concluded that the terminal region of 7q contains genes implicated in the development of the central nervous system and the caudal region. Lynch *et al*⁴⁰ further concluded that a sacral agenesis gene maps to the HPE3 holoprosencephaly

gene region at 7q36 between D7S396 and the telomere, and suggested that genes at 7q36 play a critical role in differentiation of midline mesoderm at both ends of the developing notochord. Our case, a complex of cebocephaly, alobar holoprosencephaly, cleft palate, lumbar spina bifida, sirenornelia, a single umbilical artery, and a normal chromosomal complement, adds examples of overlapping holoprosencephaly and caudal dygenesis.

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