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D P Liu, D M Burrowes and M N Qureshi

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Cyclopia: Craniofacial Appearance on MR and Three-Dimensional CT

David P. C. Liu, Delilah M. Burrowes, and M. Nasar Qureshi

Summary: In a case of alobar holoprosencephaly, a neonate who died several minutes after birth was found to have multiple facial and intracranial malformations, including cyclopia. Postmortem MR and CT findings included a single midline orbit, with two globes that contained separate lenses supplied by a single optic nerve. There were two separate superior orbital fissures and two separate lateral rectus muscles.

Index terms: Holoprosencephaly; Orbits, abnormalities and anomalies

Holoprosencephaly refers to a group of disorders arising from failure of normal forebrain development during embryonic life, with a reported frequency of approximately 0.6 per 10 000 live births (1). It includes a series of complex disorders with a broad range of severity. Cyclopia is the most severe facial malformation and is almost always seen with the alobar form of holoprosencephaly. As the disturbance leading to cyclopia occurs in early life, severe holoprosencephaly and midline disturbances are inevitable and are direct consequences of the cyclopian state. Approximately 1.05 in 100 000 births are identified as cyclopian, including stillbirths (2). We present the magnetic resonance (MR), computed tomographic (CT), and three-dimensional CT reconstruction findings of a case of cyclopia with both facial and intracranial anomalies.

Case Report

A 35-year-old pregnant woman who had been positive for the human immunodeficiency virus (HIV) for 10 years experienced spontaneous onset of contractions at 39 weeks' gestation. She reported positive fetal movement at that time. A prenatal sonogram obtained at an outside hospital showed the presence of fetal hydrocephalus with a projected poor outcome at birth. Additional history of prenatal care was not available. The mother's last CD4 count, documented 1 month prior to delivery, was in the 200s. Her history included syphilis treated in 1989 and vaginal herpes of unknown duration, inactive at the time of delivery. She was treated for endocarditis and pneumonia 5 years before the present admission. The patient was receiving zidovudine 200 mg five times a day and trimethoprim (Bactrim) every day. She had a 30 pack-year history of smoking and denied any drug or alcohol use. She had received RhoGAM (Rh_o immune globulin) during this pregnancy.

A sonogram obtained on admission showed hydramnios and fetal hydrocephalus. An infant girl was delivered by uncomplicated vaginal delivery and was found to have multiple congenital abnormalities, including a single, centrally located fused eye globe; a tusklike nose 2 cm above the eyes; a single low-lying oral cavity with minimal mouth opening; and abnormally shaped ears located low in the neck region with no external auditory canals. These abnormalities were incompatible with life and resuscitative measures were not possible. The neonate was pronounced dead several minutes after delivery.

Autopsy findings included alobar holoprosencephaly. Synophthalmia was present with a central midline orbit. The tusklike nose represented a proboscis that had no internal communication and no discernible nasal structures. The oral cavity was present but did not communicate with the gastrointestinal tract. A hypognathous jaw was present. The pinna were low lying. The external auditory canals were atretic without any communication with the temporal bone. Examination of the other systems showed a heart with a single ventricular cavity leading to the aorta and pulmonary trunk with no evidence of transposition. The remaining systems were unremarkable. Tissue at the time of autopsy was not available for genetic analysis. Polymerase chain reaction testing was done on the blood obtained from the ventricles of the fetal heart and was negative for HIV.

CT studies of the head and face were performed postmortem with thin 1-mm axial scans and reconstructed into 3-D images using an independent workstation. MR images were also obtained postmortem on a high-field-strength magnet. The intracranial structures showed classic alobar holoprosencephaly. The brain consisted of a single, unsegmented sphere with a single ventricle and no third ventricle. The falx, interhemispheric fissure, corpus callosum, and septum pellucidum were absent. The thalami

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From the Department of Radiology, Beth Israel Medical Center, First Avenue at 16th Street, New York, NY 10003. Address reprint requests to David P. C. Liu, MD.

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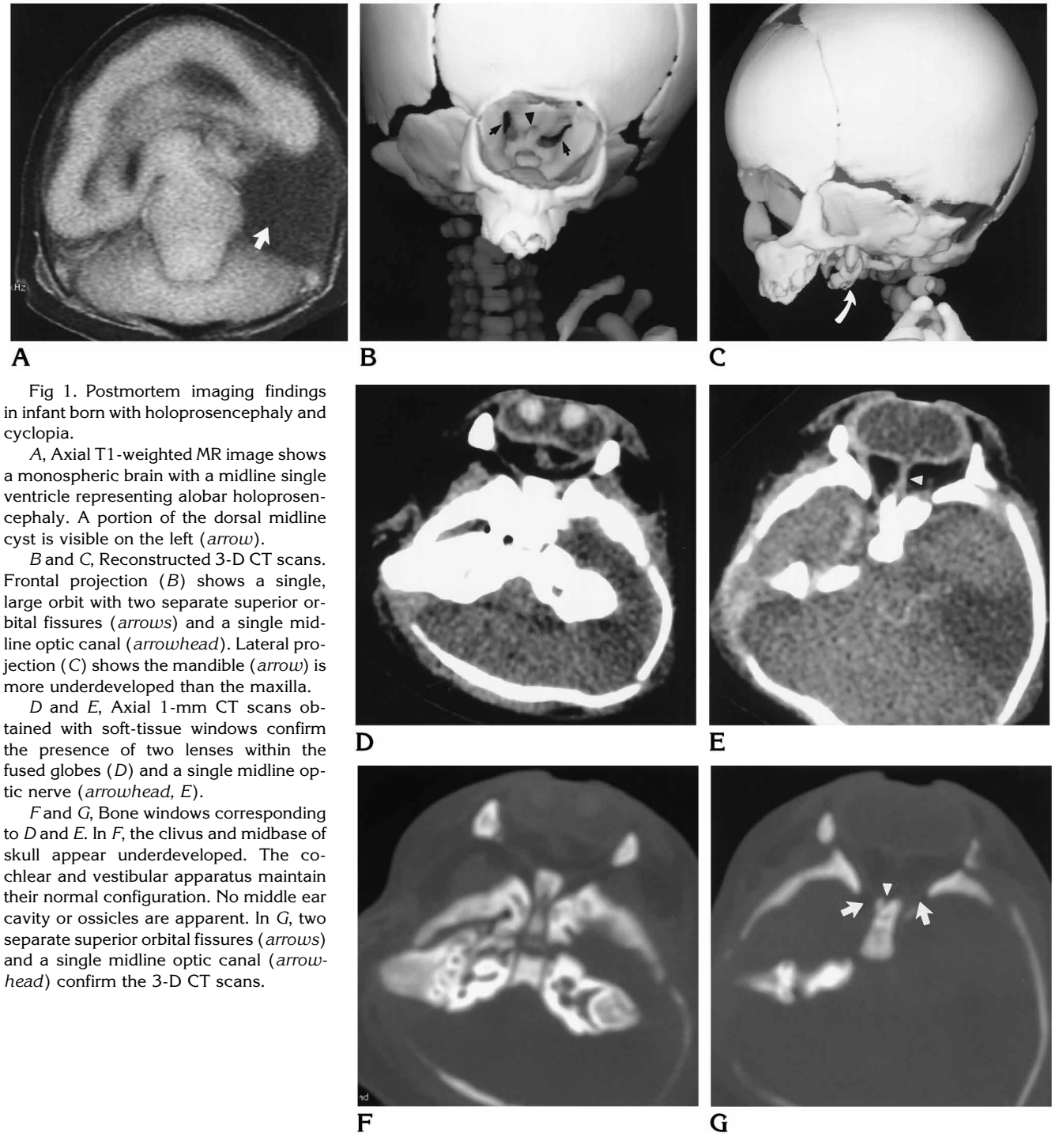

Fig 1. Postmortem imaging findings in infant born with holoprosencephaly and cyclopia.

A, Axial T1-weighted MR image shows a monospheric brain with a midline single ventricle representing alobar holoprosencephaly. A portion of the dorsal midline cyst is visible on the left (*arrow*).

B and *C*, Reconstructed 3-D CT scans. Frontal projection (*B*) shows a single, large orbit with two separate superior orbital fissures (*arrows*) and a single midline optic canal (*arrowhead*). Lateral projection (*C*) shows the mandible (*arrow*) is more underdeveloped than the maxilla.

D and *E*, Axial 1-mm CT scans obtained with soft-tissue windows confirm the presence of two lenses within the fused globes (*D*) and a single midline optic nerve (*arrowhead, E*).

F and *G*, Bone windows corresponding to *D* and *E*. In *F*, the clivus and midbase of skull appear underdeveloped. The cochlear and vestibular apparatus maintain their normal configuration. No middle ear cavity or ossicles are apparent. In *G*, two separate superior orbital fissures (*arrows*) and a single midline optic canal (*arrowhead*) confirm the 3-D CT scans.

and basal ganglia were fused, and there was a large dorsal midline cyst (Fig 1A). The most striking facial anomaly was a single midline orbit (Fig 1B and C), representing cyclopia (Fig 1D and E). The two globes contained separate lenses; however, they were supplied by a single optic nerve (Fig 1E). Two separate superior orbital fissures (Fig 1B and G) and two separate lateral rectus muscles could be identified. The proboscis, located above the single, enlarged bony orbit, consisted of areolar tissue and did not communicate with either the airway or the brain. The maxilla was hypoplastic and the mandible was severely underdeveloped (Fig 1C). Although the external auditory canals were atretic at autopsy, the temporal bones, including the inner ear structures, retained their normal configuration. The central skull base was narrow and underdeveloped with no discernible pituitary fossa or crista galli (Fig 1F).

Discussion

Holoprosencephaly is subdivided into lobar, semilobar, and alobar types, with the latter being the most severe. These major groups have characteristic clinical and radiologic features involving the brain, cranium, intracranial vasculature, and face. The intracranial findings range from a single ventricle, which is found with the alobar variety, to fully formed but mildly enlarged ventricles, which are found with the lobar type. In the alobar form, there is absence of the interhemispheric fissure, corpus callosum, and septum pellucidum, with fusion of the thalami and basal ganglia. The semilobar and lobar forms have partial to fully formed interhemispheric fissures, partial to full development of the corpus callosum, and partial to complete separation of the thalami and basal ganglia. The brain stem and cerebellum may be normal or hypoplastic in all three types. A dorsal cyst is present that ranges from large to small to absent depending on the severity of the malformation. The sagittal sinuses, vein of Galen, and internal cerebral veins range from being absent or hypoplastic to normal, corresponding to the severity of the subtype (3). The severe forms of holoprosencephaly are incompatible with life and these infants are either stillborn or live only a few hours after birth; the milder forms are compatible with life, but the survivors usually have severe mental retardation (4).

There is a strong correlation between severe facial anomalies and holoprosencephaly. Certain characteristic facial phenotypes indicate the presence and severity of holoprosencephaly. Normally, the processes of cleavage and diverticularization divide the prosencephalon into the diencephalon and telencephalon. The latter eventually grow to meet in the midline and form the falx and the interhemispheric fissure. In holoprosencephaly, the optic vesicles and the olfactory bulbs that grow out from the prosencephalon early in development are often abnormal. In alobar holoprosencephaly, the most severe form of the disease, none of these developmental processes have taken place (4). The strong correlation between median facial anomalies and anomalies of the brain in holoprosencephaly suggests an intimate embryologic relationship between the developing prosencephalon and the neural crest cells that eventually form the frontonasal process. This association can be explained by the prechordial mesoderm, which stimulates the prosencephalon to divide and migrate laterally, and also stimulates the normal development of the nose and central facial skeleton. Damage to the prechordal mesoderm, such as by mechanical, genetic, or environmental teratogens, then arrests both the prosencephalon and the midline facial bones. Failure of the optic anlage to move laterally results in synopthalmia or hypotelorism. The bizarre appearance and odd location of the proboscis can be explained by improper stimulation and lack of migration of the embryonic precursor of the nose (4). Differences in severity suggest differences in timing and susceptibility. As in our case, the mandible can also be affected (5).

The most severe forms of holoprosencephaly frequently involve the face, resulting in severe facial deformities. Facial anomalies include cyclopia, ethmocephaly, cebocephaly, and median cleft lip. This represents a spectrum in which cyclopia is the most severe malformation. Cyclopia refers to a single midline orbit that contains ocular structures that are anophthalmic, monophthalmic, or synophthalmic. A proboscis is usually present and may be doubled. It lies above the orbit, with the nasal structures and median facial bones missing. Ethmocephaly, the next most severe malformation, is the least common facial subtype and consists of severely hypoteloric orbits, usually with marked microphthalmia and a proboscis with absent nasal structure. A less severe form is cebocephaly, which consists of ocular hypotelorism and a single-nostril nose. The least severe form of facial dysmorphism includes hypotelorism, with a flat nose and a median cleft lip (3).

Orbital hypotelorism is the necessary clinical hallmark in making the diagnosis of the aforementioned facial anomalies. The diagnosis of holoprosencephaly can be suspected in the presence of orbital hypotelorism and median facial anomalies. In the pre-CT era, plain radiographs were useful in differentiating the hypotelorism of holoprosencephaly from other causes of microcrania. The absence or hypoplasia of the crista galli and subjacent nasal septum raised the probability of intracranial malformations (5). Hypognathia and agnathia, rare malformations, are additional facial features that can be associated with holoprosencephaly. Most cases of holoprosencephaly do not include agnathia, and there is no apparent connection between the severity of mandibular

underdevelopment and brain anomalies (3). The stillbirth rate is high among infants with cyclopia, and the majority are female (2).

Maternal diabetes has a well-known association with nonchromosomal-related holoprosencephaly, with a 1% risk and a 200-fold increase in fetal holoprosencephaly. Associated prenatal infections include cytomegalovirus, rubella, and toxoplasmosis. Cytomegalovirus infections have also been described with eye abnormalities, including cyclopia. Maternal oral ingestion of alcohol, salicylates, high doses of contraceptives, quinine, retinoic acid, and cortisone have been implicated, and radiation has also been suggested as a predisposing factor (6).

Zidovudine-related, dose-dependent fetal toxicity has been demonstrated in mice, causing a decrease in the litter number, decrease in size, and toxic effects related to the hematopoietic system (7). No advance effects on pregnancy have been reported in humans or experimental models as far as we know. Despite the widespread use of acyclovir, its effects on pregnancy have not been extensively studied. A review of the literature does not indicate increased adverse effects related to its use in pregnancy. Oral doses of trimethoprim have been found to produce teratogenic effects in rats, manifest as cleft palates. In some rabbit studies, the increase in fetal loss was associated with doses of trimethoprim six times the human therapeutic dose. Overall, human clinical trials have found no associated congenital anomalies in infants whose mothers had received oral trimethoprim at the time of conception or shortly thereafter (8).

There is clear-cut evidence of a genetic basis for holoprosencephaly. The evidence comes from observations of associated genetic syndromes, family studies with several affected relatives, and nonrandom chromosomal anomalies (6). Familial holoprosencephaly has been reported to show both autosomal dominant and recessive inheritance. Källén et al (2) performed an epidemiological study that associated cyclopia with other congenital malformations. In that study, infants with known chromosomal anomalies were excluded; however, most infants were not studied cytogenetically. These authors estimated that 50% of all infants with holoprosencephaly had a chromosomal anomaly, but it has been suggested that the percentage is in fact lower. The most common chromosomal anomaly associated is trisomy 13, with an overall prevalence of 1 in 17 200 births (2). Although often associated with trisomy 13, the association is not constant. As a general rule, when the patient has many extracephalic anomalies associated with holoprosencephaly, a chromosomal anomaly, such as trisomy 13, is found, whereas when the patient has few or no extracephalic anomalies, the karyotype is apt to be normal (5).

In the past, useful diagnostic studies included skull radiographs to show orbital hypotelorism and an absent crista galli, electron electroencephalography, dermatoglyphics, chromosome studies, and, sometimes, pneumoencephalography. With the advent of current techniques, such as MR imaging and CT with 3-D reconstruction, we are able to acquire better anatomic detail for more accurate categorization. The mother of the infant in this study had a variety of medical conditions, including underlying immunosuppression and exposure to a multitude of potentially toxic substances; however, no direct environmental factors could be implicated as a cause of the holoprosencephaly with cyclopia, and the precise mechanism is unclear. At present, most cases are thought to occur sporadically, with no genetic basis (3, 9). Since no genetic profile was determined in this case, a chromosomal abnormality cannot be excluded. Whenever possible, genetic analysis is advisable.

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