

Autosomal Recessive Alobar Holoprosencephaly With Essentially Normal Faces

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Holoprosencephaly is associated with a diagnostic face approximately 80% of the time. We report three siblings with alobar holoprosencephaly and essentially normal faces. A similar family was reported by Khan et al. [1970: Dev Med Child Neurol 12:71–76]. Alobar holoprosencephaly with essentially normal faces has also been observed in infants of diabetic mothers [Barr et al., 1983: J Pediatr 102:565–568]. © 2002 Wiley-Liss, Inc.

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INTRODUCTION

Alobar holoprosencephaly is typically accompanied by facial morphology that belies the brain malformation. Cyclopia, ethmocephaly, cebocephaly, and premaxillary agenesis or median cleft lip are considered “predictors” of this severe form of holoprosencephaly. Other facial changes, such as unilateral or bilateral cleft lip and hypotelorism, although less reliable predictors of underlying holoprosencephaly, are not infrequent. However, even milder facial changes, or none at all, have also been noted. Most previously reported instances of presumed recessive holoprosencephaly have had variable facial manifestations [Cohen and Gorlin, 1969]. We report three sibs who had alobar holoprosencephaly with essentially normal faces.

CASE REPORTS

Patient 1

The proposita, the first child of a 21-year-old mother and second child of a 24-year-old father, both healthy

and nonconsanguineous, was born at 40 weeks of gestation by cesarean section, weighing 3.35 kg. At 27 weeks of gestation, ultrasonography had disclosed the presence of alobar holoprosencephaly, but no other anomalies. Amniocyte karyotype was 46, XX. At birth, head circumference was 37 cm and length was 50 cm. Alobar holoprosencephaly was confirmed by computed tomography scan. Except for synophrys, no facial or extracranial anomalies were present (Fig. 1). Her course was remarkable for profound developmental delay, although she was able to see, hear, and smile, and she showed evidence of memory (anticipation of action). She never established head control or purposeful hand use. She was hypertonic when stimulated but hypotonic at rest. She had frequent episodes of irritability, occasional seizures, and marked irregularity of pulse, respiratory rate, and temperature. For the first year, her growth was normal, although feeding was difficult and time consuming. After the first year, her growth began to fall away gradually from the normal weight and length curves. The parents eventually consented to a feeding gastrostomy. At the age of 3 years and 9 months, she had a major motor seizure followed by marked brainstem dysfunction, and she died within a few days. Autopsy confirmed the presence of alobar holoprosencephaly. Brain weight was 710 g and cerebrospinal fluid (CSF) volume was 1300 mL. There was an acute hemorrhage of modest degree into the common ventricle, presumed to be an agonal event. No other abnormalities were detected.

Patient 2

A sister of patient 1 was the fourth child in the family. Two normal girls had been born in the interim. She was delivered by cesarean section at 37 weeks of gestation, weighing 3.4 kg. Ultrasonography at 4 weeks of gestation had disclosed the presence of alobar holoprosencephaly, but an otherwise normal fetal survey; amniocentesis for karyotyping was declined. At birth, her head circumference was 45.1 cm and length was 50 cm. Her face was normal. Her neonatal course was complicated by marked jaundice secondary to isoimmunization (anti-c). She had marked irregularity of pulse, respiratory rate, and temperature. She died on day 10 of

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Fig. 1. Patient 1 at 4 months of age.

life. Autopsy confirmed the presence of alobar holoprosencephaly and hydrocephaly. Brain weight was 165 g and CSF volume was 950 mL. No other anomalies were detected. Testing for a sonic hedgehog mutation in the baby and her parents showed no mutation. (M. Muenke, personal communication).

Patient 3

A brother of patients 1 and 2 was delivered by cesarean section at 39 weeks of gestation, weighing 3.21 kg. Ultrasonography at 16 weeks of gestation had disclosed the presence of alobar holoprosencephaly and no other anomalies. At birth, his head circumference was 33 cm and length was 49 cm. He had mild hypotelorism by measurement (inner canthal distance 19 mm, outer canthal distance 58 mm). Otherwise his face was normal (Fig. 2), and there were no extracranial anomalies. His neonatal course was complicated by jaundice secondary to isoimmunization, with the jaundice visually clearing by 8 days. His weight and length proceeded along the normal curves, but his head circumference gradually dropped from the 5th centile to less than the 2.5 centile. His postnatal course was marked by developmental delay, but like his older sister he could see, hear, smile, and show evidence of memory. He also had episodic bouts of irritability, minimal seizure activity (controlled by sodium valproate), and irregularity of pulse, respira-



Fig. 2. Patient 3 at 1 day of age.

tory rate, and temperature. At 7 and 8 months of age, two successive bouts of bronchiolitis led to his death. No autopsy was performed.

DISCUSSION

The finding of three affected sibs in this family is compatible with autosomal recessive inheritance. Many authors have established autosomal recessive inheritance in holoprosencephaly, and the subject has been reviewed elsewhere [Cohen and Gorlin, 1969; Cohen et al., 1971; Cohen, 1989b; Cohen and Sulik, 1992]. What is striking in our cases, however, is that three affected siblings had alobar holoprosencephaly with minimally dysmorphic faces. All three children had midline upper lip frenula, and the older child had normal incisoral morphology. Examination of both parents for lip, palate, dental, and ocular clues of midline developmental aberration was unrevealing.

Alobar holoprosencephaly with a normal or mildly dysmorphic face, not diagnostic of the brain malformation, has been recorded previously [Roach et al., 1975; Cohen, 1989a, 1989b], but the overwhelming majority of such cases have been sporadic. Only in the family reported by Khan et al. [1970] were there four affected siblings with essentially normal faces. Romshe and Sotos [1973] reported three siblings—two with holoprosencephalic faces and the other with a normal face,

short stature, and hypothalamic–pituitary dysfunction. Alobar holoprosencephaly with an essentially normal face has also been observed in infants of diabetic mothers [Barr et al., 1983]. Cohen [1989a], using the data of Roach et al. [1975], estimated that the face is nondiagnostic in approximately 20% of infants with alobar holoprosencephaly. In an additional set of infants and fetuses with karyotypically normal alobar holoprosencephaly collected by the University of Michigan Teratology Unit and colleagues, 18% had nondiagnostic faces.

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