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Holoprosencephaly in an 8.5-week triploidy gestation

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Introduction

Holoprosencephaly (HPE), the most common malformation of the human forebrain, is because of failed midline cleavage of the developing forebrain between the 18th and 28th days of gestation. HPE occurs in up to one in 250 gestations, though less than 3% of these survive to birth (Matsunaga and Shiota, 1977; Leoncini *et al.*, 2008). Severity is defined by the extent of brain malformations; categories include alobar (the most severe type), semilobar, and lobar HPE (Plawner *et al.*, 2002). The spectrum of facial dysmorphisms is wide, but at the severe end of the spectrum, individuals may show cyclopia or synophthalmia (fusion of the optic vesicles with incomplete eye development), a proboscis (a tubular nasal appendage above the fused eyes), and severe microcephaly. HPE may occur as one feature in a syndrome (as in Smith-Lemli-Opitz syndrome) (Kelley *et al.*, 1996), result from teratogenic influences (such as the use of cholesterol lowering agents in early gestation) (Edison and Muenke, 2004), or be because of mutations in genes involved in forebrain development (such as *SHH*) (Muenke and Beachy, 2000). Most often, HPE occurs in the context of cytogenetic anomalies. Up to 50% of patients born with HPE have cytogenetic anomalies; an even greater proportion of fetuses with HPE have cytogenetic anomalies (Muenke and Beachy, 2000).

Common findings in triploidy include limb anomalies, microcephaly, and neural tube defects (Philipp *et al.*, 2004). Cases of HPE with triploidy have been described earlier, though no diagnosis was made as early in gestation as the case described here (Wong *et al.*, 1999; Hsu *et al.*, 2001; Philipp *et al.*, 2004). We present a case of HPE in which the chromosome analysis on the embryo revealed triploidy (69,XXX), and where an unusually well-defined photograph showing the dysmorphic appearance of the embryo is available.

Clinical report

The embryo (Fig. 1) was the product of conception of an 8.5-week gestation with embryonic demise in the context of a missed abortion. On examination, the chorionic vesicle was initially intact. The crown-rump length measured 1.8 cm (consistent with 8-8.5 weeks gestation). Hypotelorism was striking, as evidenced by the position of retinal pigment, and a proboscis was present in the midline above the retinal pigment. There were no appreciable nasal pits or mouth. The fingers were webbed but distinct, and footplates were present, but there were no toe rays. Dating by measurements and embryological development was thus consistent with 44-48 postmenstrual days (30-34 days postfertilization).

Other than the dysmorphic facial features, no additional anomalies were identified. The embryo was too macerated to delineate details of central nervous system findings. However, because of the severe facial dysmorphisms, the HPE type was presumed to be alobar. Chromosome analysis on the fetus revealed triploidy (69,XXX) without evidence of mosaicism.

Discussion

Although HPE is common, HPE in the presence of triploidy is not often reported, and it is unusual for the diagnosis to be made so early in gestation. The ability to observe the dysmorphic features in HPE before 9 weeks gestation is extremely rare, and provides a fascinating depiction of the earliest stages of the facial dysmorphisms in severe HPE (Yamada *et al.* 2004).

This case highlights the importance of vigilance for fetal anomalies, as the diagnostic approach will differ. Traditionally, many clinicians do not request testing on products of conception unless there is a history of recurrent spontaneous abortions, but the presence of dysmorphic features or congenital anomalies should alter the testing strategy. Chromosome analysis or more specific genetic testing may be warranted in such cases, and to establish a diagnosis and order appropriate testing, it is vital to be able to recognize anomalies even in the very early stages of development.

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Fig. 1.
Frontal and profile views of embryo at 8.5 weeks gestation, with hypotelorism (as evidenced by closely spaced retinal pigment), microcephaly, and a proboscis structure above the developing eyes.