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Holoprosencephaly due to Numeric Chromosome Abnormalities

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Abstract

Holoprosencephaly (HPE) is the most common malformation of the human forebrain. When a clinician identifies a patient with HPE, a routine chromosome analysis is often the first genetic test sent for laboratory analysis in order to assess for a structural or numerical chromosome anomaly. An abnormality of chromosome number is overall the most frequently identified etiology in a patient with HPE. These abnormalities include trisomy 13, trisomy 18, and triploidy, though several others have been reported. Such chromosome number abnormalities are almost universally fatal early in gestation or in infancy. Clinical features of specific chromosome number abnormalities may be recognized by phenotypic manifestations in addition to the HPE.

Keywords

Holoprosencephaly; HPE; Chromosome Anomalies; Trisomy; Triploidy

INTRODUCTION

In patients with holoprosencephaly (HPE), the first genetic study sent for laboratory testing is almost universally a routine chromosome analysis. Chromosomal anomalies in patients with HPE detectable either by conventional karyotyping or by newer technologies such as microarray can involve virtually any chromosome. Abnormalities of chromosome number are particularly common [Muenke and Beachy, 2001]. Estimates of abnormalities of chromosome number range from 32–41% of patients with HPE [Bullen et al., 2001; Ong et al., 2007; Goetzinger et al., 2008]. Notably, these gross chromosomal anomalies frequently result in a nonviable fetus, and thus tend to be overrepresented in patients ascertained due to anomalies appreciated in utero. However, the vast majority of conceptions with large imbalances such as trisomy or monosomy are not viable and, therefore, the presence of HPE in these conceptions may be underestimated. While survivors with HPE are less likely to have such a large genomic imbalance, laboratory analysis may instead identify milder genomic imbalances or molecularly-detectable mutations in HPE-associated genes.

The purpose of our review is to provide a summary of the knowledge of the chromosomal causes of HPE.

TYPES OF CHROMOSOME NUMBER IMBALANCES

Trisomy 13 accounts for up to 75% of cases of patients with HPE due to all chromosomal anomalies (including cryptic rearrangements) and triploidy for up to 20%, while trisomy 18 is much less commonly seen in conjunction with HPE, and accounts for 1–2% of cases [Ong et al., 2007; Goetzinger et al., 2008]. HPE has also been reported in patients with trisomies other than trisomies 13 and 18, including a small number with trisomy 21 [Lehman et al., 1995; Bullen et al., 2001; Papp et al., 2006; Ong et al., 2007; Goetzinger et al., 2008]. While aberrant signaling related to abnormal copy numbers of HPE-related genes located on some of these chromosomes may plausibly result in HPE, some of these cases, such as those involving patients with trisomy 21 and HPE, may be coincident [Epstein et al., 1988].

Clearly, HPE is a common feature of trisomy 13. HPE has been reported in 17–39% of patients with trisomy 13 [Lehman et al., 1995; Papp et al., 2006; Lin et al., 2007]. While HPE due to trisomy 13 is often detected prenatally by ultrasound, this technique is obviously not as sensitive as pathologic examination. When pathological examination is performed about 67% of patients with trisomy 13 have signs of forebrain anomalies consistent with HPE [Moerman et al., 1988].

Prenatally-detected central nervous system (CNS) malformations appreciable on ultrasound are strongly associated with and predictive of chromosomal abnormalities, especially trisomies 13 and 18. In addition to HPE, many other types of CNS malformations may be observed. In one large review of patients with trisomies 13, 18, and 21, of the many types of possible neurological anomalies, when isolated, only HPE, spina bifida, and agenesis of the corpus callosum were significantly associated with trisomy 13, while anencephaly was significantly associated with trisomy 18 [Goetzinger et al., 2008]. As detailed below, the presence of *ZIC2* on chromosome 13 and the association of this gene with both HPE and HPE-spectrum anomalies (which include corpus callosal agenesis), along with an increased frequency of neural tube defects seen with abnormalities chromosome 13, warrants further investigation [Ballarati et al., 2007].

Importantly, other anomalies in addition to neurological and facial features consistent with HPE are found in all fetuses with chromosome number anomalies [Bullen et al., 2001; Bekdache et al., 2009]. Thus, the presence of multisystem organ anomalies and other features in addition to facial and neurological abnormalities are a clue that frank cytogenetic abnormalities are causative.

BIOLOGIC AND RESEARCH IMPLICATIONS

A clear biological mechanism by which abnormalities of chromosome number can cause HPE has not been delineated, but it is intriguing that *ZIC2* and *TGIF* are located at chromosomes 13q32 and 18p11.2, respectively, and that aberrant (admittedly, loss-of-function) signaling involving these genes are among the relatively common causes of human HPE [Roessler et al., 2009; El-Jaick et al., 2007]. Multiple interacting factors located on these chromosomes likely play a role in forebrain formation, and large-scale copy number changes involving more than a single gene could interrupt key signaling pathways.

There are rare cases of (mosaic) trisomy 9 in patients with HPE [Gerard-Blanluet et al., 2002]. Interestingly, HPE-causing mutations in the *PTCH1* gene, located at 9q22.3, are thought to result in HPE by a gain-of-function mechanism affecting Sonic Hedgehog signaling (*PTCH1* normally acts to repress *SHH* signaling) [Ming et al., 2002]. Trisomies and triploidy, which result in large copy-number gains, could overall repress integral signaling pathways, such as *SHH*, necessary for normal forebrain development.

COUNSELING ISSUES

Both trisomy 13 and trisomy 18 are associated with advanced maternal age [Crider et al., 2008]. Triploidy presents a more complex and controversial situation with respect to mechanism and parental origin [Zaragoza et al., 2000; McFadden and Langlois, 2000]. While advanced maternal age is generally not considered to be a major factor, it may play a role in some cases of triploids, presumably only digynic ones [McFadden and Langlois, 2000; Forrester and Merz, 2003]. A combination of sonographic and maternal serum testing can screen for trisomy 13 and 18. Triploidy may be detected by maternal serum screening, although the scope of sonographically detectable fetal anomalies in triploidy can be quite variable depending upon whether the extra set of chromosomes was inherited from the mother or the father. As outlined in the Table, all conditions have a reduced survival rate outside of the immediate neonatal period, though advances in neonatal care may prolong survival. It is critical that families are appropriately counseled regarding prognostic implications. The association of triploidy with molar pregnancies raises additional counseling implications regarding maternal health [Bekdache et al., 2009].

Most cases of abnormalities of chromosome number are isolated occurrences. However, recurrent cases have been reported, including triploidy [Brancati et al., 2003]. Overall, the recurrence risk of HPE due to cytogenetic anomalies is estimated at 1% [Peebles, 1998].

DISCUSSION

Chromosome number anomalies are relatively common causes of HPE. As the understanding of the molecular pathogenesis of HPE increases, coupled with the advancement of new testing modalities, new diagnostic tests continue to become available. This growing complexity can complicate diagnostic decision-making for clinicians encountering patients with disorders such as HPE. However, it is important to remember that chromosome analysis, one of the older diagnostic tests, is still the most efficient, highest-yield, and most affordable first option for most scenarios when a clinician encounters a patient with HPE, whether it be in the obstetric, neonatal, or pediatric setting. In fact, before other specific molecular diagnoses are entertained, it is important to exclude cytogenetic abnormalities especially anomalies of chromosome number 13 and 18.

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Table I

Features of conditions of numeric chromosome abnormalities which are associated with HPE^a.

	Trisomy 13	Trisomy 18	Triploidy
Prevalence <i>among recognized conceptions</i> ^{b,c}	1/5,000	1/2,000	1/22,000
Livebirth prevalence ^{b,c}	1/11,000	1/7,000	<1/450,000
HPE incidence	Up to 39% ^d	Rare	Rare
Median survival for liveborn infants	7 days	7 days	<24 hours
Other cardinal features	Deafness, microcephaly, cleft lip/palate, capillary angiomas, polydactyly, cardiac defects, genital defects	Prominent occiput, clenched hand, with 2 nd digit overlapping over 3 rd and 5 th over 4 th , cryptorchidism, congenital heart defects	Large placenta, growth restriction, hypertelorism and eye defects, cardiac, genital defects

^aData summarized from Smith's Recognizable Patterns of Human Malformations and Carey [2005] except where otherwise noted.

^b[Crider et al., 2008; Cragan and Gilboa, 2009].

^dSubtle midline forebrain anomalies appreciable on pathologic examination may occur at an even higher frequency [Moerman et al., 1988].