Hypertelorism

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Introduction

Hypertelorism is rarely an isolated finding but is associated most commonly with other major abnormalities that are often syndromic. Hypertelorism can also be caused by physical destruction of the facial midline structures, such as by a wide facial cleft, bifid broad nose, or amniotic bands.

Definition

Hypertelorism is defined as an interocular distance of >95th percentile for gestational age.[1]

Ultrasound Findings

The coronal view of the fetal face is the best way to evaluate the orbits. The modified coronal view, which shows the upper lip, nose, and lower orbits and is similar to the view used to visualize a facial cleft, is also useful for assessment of the orbits. Charts are available for normative data of the outer-to-outer and inner-to-inner orbital diameters, although most often hypertelorism is not subtle. Isolated hypertelorism almost never is detected in utero; other facial, intracranial, cranial, or syndromic abnormalities are almost always present (Figure).

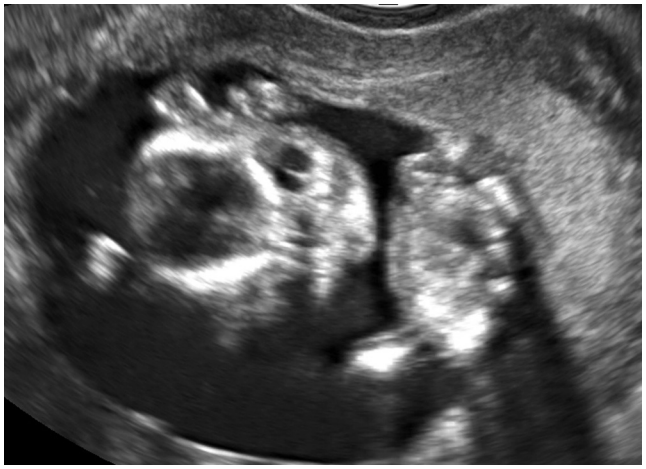
Associated Abnormalities

Hypertelorism usually occurs because of physical separation of orbits, as with a wide facial cleft, frontonasal dysplasia (midline facial defects, bifid or broad nose that results in hypertelorism), or an anterior encephalocele or amniotic band sequence. There are hundreds of genetic conditions that have hypertelorism as a feature. Neonatal ophthalmologic abnormalities have also been described.

Syndromes that are associated with hypertelorism include Noonan syndrome (cystic hygroma, hydrops), skeletal dysplasias (camptomelic dysplasia, chondrodysplasia punctata), Larsen syndrome (limb abnormalities including dislocations and hyperextensions at knee joints), multiple pterygium syndrome (multiple contractures and webbing across the joints), Roberts (pseudothalidomide) syndrome, craniosynostosis syndromes (Apert, Crouzon, and Pfeiffer), Pena Shokeir syndrome (multiple joint contractures, facial anomalies), Opitz BBB syndrome (hypertelorism with hypospadias), and CHARGE association (Coloboma, Heart defects, Atresia choanae [choanal atresia], growth Restriction, Genital anomalies, and Ear anomalies).

Chromosomal abnormalities that feature hypertelorism include 4p deletion (Wolf-Hirschhorn syndrome), 9p duplication, tetrasomy 12p (Pallister-Killian syndrome), triploidy, and trisomy 18.[2,3]

FIGURE
Hypertelorism in a fetus with triploidy at 14 weeks of gestation



Note the characteristic large head and small body. The eyes are very wide apart even without measurement of the interocular distance.

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Differential Diagnosis

In addition to the aforementioned genetic causes, the orbits may be distorted or displaced by masses, such as an intracranial teratoma (associated with an intracranial component) or glioma (small mass at the medial aspect of the orbit that displaces the orbit laterally) or by amniotic bands.

Genetic Evaluation

Diagnostic testing (amniocentesis or chorionic villus sampling) with chromosomal microarray analysis (CMA) should be offered when hypertelorism is detected. If ultrasound findings or screening test results are suggestive of a common aneuploidy, it is reasonable initially to perform karyotype analysis or fluorescence in situ hybridization, with reflex to CMA if these test results are normal. If there are additional anomalies, consanguinity, or a family history that is suggestive of a specific genetic disorder, gene panel testing or exome sequencing is often useful because CMA does not detect single-gene (Mendelian) disorders and such genetic disorders are common with hypertelorism. If exome sequencing is pursued, appropriate pretest and posttest counseling by a provider who is experienced in the complexities of genomic sequencing is recommended.[4] After appropriate counseling, cell-free DNA screening is an option for patients who decline diagnostic evaluation.

Pregnancy and Delivery Management

A detailed ultrasound examination should be performed and should include comprehensive imaging of the intracranial structures (eg, a neurosonogram) and the fetal heart with consideration of a fetal echocardiogram, given the frequent association with syndromes that include congenital heart defects and intracranial abnormalities. Referrals to pediatric ophthalmology, craniofacial clinic, plastic surgery, or other subspecialty services should be based on additional sonographic findings. Fetal magnetic resonance imaging and a pediatric neurology consult are indicated if intracranial anomalies are suspected. Pregnancy termination is an option that should be discussed with all patients in whom a fetal anomaly is detected. Shared patient decision-making requires a thorough evaluation and multidisciplinary counseling regarding prognosis. The specific finding of hypertelorism does not generally affect delivery management, although delivery at a tertiary care center with pediatric genetic, craniofacial, and ophthalmology services should be considered, as appropriate for the clinical findings.

Prognosis

Isolated hypertelorism can be physiologic, although hypertelorism that appears to be isolated prenatally may be diagnosed as a syndrome in the neonatal period. Surgical correction may be indicated for cosmetic purposes or in cases of craniosynostosis. The long-term outcome is based on the underlying cause and the complexity of associated findings. Counseling is often driven by associated structural anomalies or a syndromic diagnosis. Cytogenetic and molecular diagnosis can assist with prognostic counseling.

Summary

Hypertelorism refers to increased interorbital distance. It usually is associated with a syndrome but can also be isolated or caused by mass effect. Prenatal evaluation should include an assessment for associated anomalies to guide genetic testing and prognostic counseling. Diagnostic testing with karyotype analysis, CMA, and/or gene panel or exome testing should be considered. No change in route of delivery is needed, although delivery at a tertiary care center with pediatric subspecialty services may be indicated. ■

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