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DEVELOPMENTAL DISORDERS

CAUSES OF CONGENITAL MALFORMATIONS

The genetic epidemiology of congenital malformations (CMs) and interaction with environmental causes are reviewed from the Arkansas Center for Birth Defects, Arkansas Children's Hospital, Little Rock, AS. CMs affect 3% to 4% of all live births. In the US, 150,000 infants are born yearly with birth defects. CMs and genetic diseases are the leading cause of infant mortality. Most CMs have a multifactorial etiology, resulting from an interaction between genetic and environmental factors. Familial aggregation patterns are often inconsistent with simple mendelian inheritance patterns. Reasons for the inconsistent familial clustering of CMs include incomplete penetrance, variable expressivity, and genetic heterogeneity. Twin studies used to determine the importance of genetic factors in the etiology of CMs have limitations due to various factors, including insufficient numbers of twins with birth defects, and difficulties in establishing zygosity. The selection of candidate genes contributing to CMs, an important step in genetic epidemiology, can be accomplished by associating the gene with biological processes, such as genetic polymorphisms in the folate metabolic pathway and risk of neural tube defects. The long arm of chromosome 22 (22q11.2) is a critical region for examining candidate genes and the relation of chromosome deletions to variation in clinical manifestations of CMs. A genome-wide scan using linkage analysis is another way to identify a candidate gene involved in the cause of the birth defect. Linkage disequilibrium (allelic association) between a genetic marker allele and the gene causing the malformation suggests that the two are closely approximated on the same chromosome.

Possible synergistic effects of environmental factors with the gene allele or multiple low-penetrance alleles may determine the occurrence of a CM when a single factor may not. Case-controlled studies comparing cases with a CM and unrelated healthy controls are subject to bias and require large sample sizes. Genomic control and structured association are recently proposed methods to avoid the limitations of population-based studies. Family-based studies control for genetic background. The interview date and banked DNA of 35 birth defect categories compiled by the National Birth Defects Prevention Study (NBDPS) since

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1997 will facilitate future research on the etiology of CMs. (Hobbs CA, Cleves MA, Simmons CJ. Genetic epidemiology and congenital malformations: From the chromosome to the crib. Arch Pediatr Adolesc Med April 2002;156:315-320). (Reprints: CM Hobbs MD, PhD, Dept Pediatrics, University of Arkansas, 11219 Financial Ctr Parkway, Ste 250, Little Rock, AR 72211).

COMMENT. The identification of genes and environmental factors involved in the etiology of congenital malformations will aid in the prevention, diagnosis, prognosis, and treatment of congenital malformations.

A Neuropathological Approach to the classification and cause of genetic defects and specifically *holoprosencephaly* is provided by Sarnat HB and Flores-Sarnat L at Cedars- Sinai Medical Center, Los Angeles, CA (J Child Neurology 2001;16:918-931). The need for a new classification for holoprosencephaly is suggested that integrates morphological and genetic criteria. Genes expressed in the neural tube may have rostrocaudal and mediolateral gradients in axes other than the vertical. A rostrocaudal gradient extending to the mesencephalic neuromere may affect the development of the bones of the face and explain the midfacial hypoplasia seen with holoprosencephaly. Four defective genes have been identified, three having a ventrodorsal gradient of expression (*SHH, SIX3, and TGIF*) and one a dorsoventral gradient (*ZIC2*).

Sarnat HB and associates also report 2 infant cases of **agenesis of the mesencephalon and metencephalon with certebellar hypoplasia**, a rare congenital malformation resulting in early death from impaired central respiratory drive (Pediatric and Developmental Pathology 2002;5:54-68). The authors speculate that the defect results from a mutation or deletion in the *EN2* gene.

CHIARI TYPE I MALFORMATION AND SEIZURES

Four children with epilepsy, ranging in age from 8 to 15 years, and diagnosed with Chiari type I malformation by brain magnetic resonance imaging (MRI), are reported from La Sapienza University, Rome, Italy. Seizures were complex partial, and the EEG showed temporal and parieto-occipital sharp waves or spikes. Headaches occurred in one child. The MRI showed no cortical structural involvement compatible with epileptogenic dysgenesis. An interictal SPECT showed cortical areas of hypoperfusion that correlated with the EEG focal abnormalities. A cerebellar hypoperfusion was also shown in 2 of the patients, suggesting an associated functional or structural lesion. (Iannetti P, Spalice A, Ciccoli C De F, et al. Seizures in paediatric Chiari type I malformation: the role of single-photon emission computed tomography. Acta Paediatr 2002;91:313-317). (Respond: P. Iannetti MD, Pediatric Neurology Department, La Sapienza University, Viale Regina Elena, 324, IT-00161 Roma, Italy).

COMMENT. Headache and neck pain are the most common symptoms associated with Chiari I malformation in childhood,. and seizures are infrequently reported. The MRI of the cerebrum is usually normal, and seizures are assumed to be cryptogenic. Brain SPECT, revealing a functional or structural lesion, appears to offer a cortical and/or cerebellar explanation for the seizures in some cases, when the MRI evidence for microdysgenesis is lacking.