

# PEDIATRIC NEUROLOGY BRIEFS

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### CONGENITAL MALFORMATIONS

#### **HOLOPROSENCEPHALY VARIANT**

The clinical manifestations in 15 patients (6 boys and 9 girls) with middle interhemispheric variant (MIH) of holoprosencephaly (HPE) were compared with classic subtypes (alobar, semilobar, and lobar) of HPE in a multicenter study at Stanford University School of Medicine and Lucile Packard Children's Hospital; Children's Hospital of Philadelphia; University of California at San Francisco; Texas Scottish Rite Hospital, Dallas; and Kennedy Krieger Institute, Baltimore, MD. The neuroimaging and clinical data were compared with those of 68 patients with classic HPE. The mean age at time of evaluation was 3.8 years (range 0.5 to 14 years). Endocrinopathy occurred in none of the patients with MIH cf to 72% of those with classic subtypes of HPE ( $p < 0.0001$ ). Six patients (40%) had seizures, 4 (67%) had a dorsal cyst and hydrocephalus requiring shunting and correlating with thalamic nonseparation, 7 (47%) were microcephalic, 3 had cleft lip and/or palate dysmorphism. Spasticity was the most common motor abnormality, occurring in 12 (86%), an incidence similar to that found in other HPE subtypes. Hypotonia occurred in 8 (57%), dystonia in 7 (50%), and none had choreoathetosis (cf to 41% affected in semilobar HPE [ $p < 0.0039$ ]). None had caudate or lentiform nuclei abnormalities on MRI. Mobility, upper extremity function, and language of the MIH group were similar to the lobar HPE classic type. (Lewis AJ, Simon EM, Barkovich AJ et al. Middle interhemispheric variant of holoprosencephaly. A distinct cliniconeuroradiologic subtype. *Neurology* December (2 of 2) 2002;59:1860-1865). (Reprints: Dr Jin S Hahn, Department of Neurology, A343, 300 Pasteur Drive, Stanford, CA 94305).

COMMENT. The middle interhemispheric variant (MIH) of holoprosencephaly (HPE) is similar to the classic lobar subtype of HPE in terms of functional motor development and language, but differs in the absence of endocrine dysfunction and choreoathetosis.

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Holoprosencephaly is a congenital malformation dating to the first 4 weeks of embryogenesis and caused by a defect in patterning of the basal forebrain, with incomplete separation of the cerebral hemispheres and basal ganglia. The 3 classic subtypes of HPE, alobar, semilobar, and lobar, are based on the degree of hemispheric separation. A fourth subtype, MIH, is characterized by nonseparation of the posterior frontal and parietal regions of the cerebral hemispheres, whereas more polar areas of the cerebrum, basal forebrain, anterior frontal lobes, and occipital regions, are fully cleaved. MIH cases also have normal separation of the lentiform nuclei and hypothalamus, correlating with the absence of choreoathetosis and normal endocrine function, including temperature regulation, in this subtype of HPE. The thalamus is the most commonly affected deep gray nucleus in MIH, with nonseparation in 33% of cases. This mainly topographical classification of CNS malformations is being replaced by a new classification based on the integration of morphological and molecular genetic criteria, as proposed by Sarnat HB and Flores-Sarnat L, 2001 (see *Ped Neur Briefs* August 2001;15:57). MIH is thought to be caused by impaired induction or patterning of the embryonic roof plate, and is sometimes related to ZIC2 mutations.

In an editorial, Patterson MC of Columbia University, Neurological Institute, NY, emphasizes the associated facial dysmorphism as a reflection of the severity of the brain malformation in HPE (Holoprosencephaly, the face predicts the brain; the image predicts its function. *Neurology* Dec (2 of 2) 2002;59:1833-1834). Gross facial malformation such as a single eye (cyclopia) is predictive of the most severe alobar type of HPE, whereas mild to moderate facial dysmorphism (cleft lip or palate, hypertelorism) corresponds with the milder MIH subtype or an asymptomatic carrier state for HPE. A high incidence of delayed myelination has been found in children with classical HPE, whereas MIH cases have normal myelination, appropriate for age, as described in the following article (Barkovich AJ et al. 2002).

## WHITE MATTER MATURATION IN HOLOPROSENCEPHALY

White matter maturation in holoprosencephaly (HPE) was assessed by MRI scans in 47 patients (age 1 day to 16 years, median age 7 months) evaluated at the University of California, San Francisco. White matter maturation was delayed in 25 of 47 patients, and was easier to detect in infants compared to older children (24/32 affected <1 year of age, 1/15 >1 year of age). The classic severe subtypes of HPE were especially involved (2/4 lobar, 20/31 semilobar, 3/6 alobar), whereas 0/6 with MIH had myelin delay. The classic and MIH variants of HPE appear to have different patterns of myelination, reflecting different underlying causes. (Barkovich AJ, Simon EM, Glenn OA et al. MRI shows abnormal white matter maturation in classical holoprosencephaly. *Neurology* Dec (2 of 2) 2002;59:1968-1971). (Reprints: Dr AJ Barkovich, Division of Neuroradiology, L 371, University of California, 505 Parnassus Ave, Box 0628, San Francisco, CA 94143).

COMMENT. Infants with classic holoprosencephaly (HPE) have delayed white matter maturation. HPE results from abnormal development of the floor plate and ventral neural tube, at the level of the prosencephalon, and oligodendrocytes, involved in myelin production, originate in the ventral aspect of the neural tube close to the floor plate. These