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CONGENITAL MALFORMATIONS

PATHOGENESIS OF CHIARI II MALFORMATION

Ependymal vimentin immunoreactivity was studied in necropsy specimens of brains and spinal cords of 14 patients with Chiari II malformations and 2 with congenital aqueductal stenosis without Chiari malformation at Cedars-Sinai Medical Center and UCLA School of Medicine, Los Angeles, CA. Ages ranged from 20-weeks gestation to 48 years. In the fetus and young infant with Chiari II malformation, aqueductal stenosis, and hydromyelia, vimentin was focally upregulated in the ependyma only in areas of dysgenesis. Glial fibrillary acidic protein (GFAP) and S-100B protein expressions were normal. Vimentin upregulation was also present in ependymal remnants of the congenital atretic cerebral aqueduct, unassociated with Chiari malformation. In older children and adults with Chiari II malformation, vimentin overexpression was more generalized and nonspecific and included the ependyma of the lateral ventricles. Vimentin is probably not involved directly in the pathogenesis of Chiari II malformation but may reflect a secondary upregulation and defective expression of another gene. The findings support the hypothesis of a molecular genetic defect in the etiology of Chiari II malformation rather than a mechanical cause. (Sarnat HB. Regional ependymal upregulation of vimentin in Chiari II malformation, aqueductal stenosis, and hydromyelia. *Pediatr Dev Pathol* 2004;7:48-60). (Respond: Harvey B Sarnat MD, Cedars-Sinai Medical Center, 4221 North Tower, 8700 Beverly Boulevard, Los Angeles, CA 90048).

COMMENT. The prevailing theories of pathogenesis of Chiari malformations postulate mechanical mechanisms. These include the traction theory due to a tethered spinal cord, the pulsion theory with pressure on the fourth ventricle from fetal hydrocephalus, insufficient accumulation of CSF to distend the cerebral vesicles and posterior fossa, and a crowding theory in which a small posterior fossa and rapid growth of neural tissue leads to

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herniation of the brainstem through the foramen magnum. Sarnat proposes a molecular genetic theory of pathogenesis due to mutation of candidate genes such as HOX, WNT, and PAX, with ectopic expression in the embryonic hindbrain. Vimentin immunoreactivity in the ependyma may provide a useful marker of focal abnormality in the fourth ventricle and aqueduct in fetuses and infants with congenital hydrocephalus.

Chiari I malformation and neurofibromatosis type 1. Two large groups of pediatric patients at the Children's Hospital, University of Alabama, Birmingham, AL were examined retrospectively to determine the significance of an association of these conditions. Of 130 surgically treated Chiari I malformations (Group 1), 5.4% also had neurofibromatosis type 1. Of a second group of 198 patients seen in the neurofibromatosis clinic and who underwent neuroimaging, 8.6% had a concomitant Chiari I malformation. The authors hypothesize that the same early dysgenesis of mesoderm responsible for Chiari I malformation may also account for neurofibromatosis type 1. (Tubbs RS, Rutledge SL, Kosentka A, et al. **Pediatr Neurol** 2004;30:278-280).

For further accounts of recent advances in cerebral dysgenesis, see Sarnat HB, in **Progress in Pediatric Neurology III**, PNB Publishers, 1997;365-369; Sarnat HB. Gene table. CNS malformations: gene locations of known human mutations. **Eur J Pediatr Neurol** 2004;8:105-108; and Sarnat HB. Watershed infarcts in the fetal and neonatal brainstem. An etiology of central hypoventilation, dysphagia, Mobius syndrome and micrognathia. **Eur J Pediatr Neurol** 2004;8:71-87.) Also, see Sheen VL, Basel-Vanagaite L, Goodman JR, et al. Etiological heterogeneity of familial periventricular heterotopia and hydrocephalus. **Brain Dev** 2004;26:326-334. One pedigree had a known FLNA mutation with hydrocephalus and valproate exposure during pregnancy. Most neural tube defects arise from multifactorial causes, with interactions between genetic and environmental factors.

FAMILIAL CONGENITAL FACIAL PALSY

Three males with congenital facial palsy from 3 generations in the same family are reported from the Floating Hospital for Children, Tufts-New England Medical Center, Boston, MA. Each had a left facial palsy, more severe in successive generations. The proband, a 9-year-old male, and his father had abnormal MRI studies, with enlargement and/or enhancement of the tympanic portion of the facial nerve. Taste in the anterior two thirds of the tongue was preserved, and blink reflexes were asymmetric. EMG/nerve conduction studies confirmed the nerve palsy and showed lowered compound muscle action potential amplitudes. The etiology was undetermined. (Kondev L, Bhadelia RA, Douglass LM. Familial congenital facial palsy. **Pediatr Neurol** 2004;30:367-370). (Respond: Dr Kondev, Floating Hospital for Children at Tufts-New England Medical Center, Division of Pediatric Neurology, 750 Washington St, Tufts-NEMC #330, Boston, MA 02111).

COMMENT. This appears to be the first report of familial congenital facial palsy. A partial agenesis of the facial nerve nucleus is considered in etiology. In the absence of an associated sixth nerve palsy, a diagnosis of Mobius syndrome is unlikely.