GENETIC/ENVIRONMENTAL INFLUENCES IN FRAGILE X DISEASE

The genetic and environmental factors influencing cognitive outcomes in 120 children (80 boys and 40 girls) with the fragile X full mutation and their unaffected siblings were determined by in-home evaluations and reported from the Departments of Psychiatry and Pediatrics, Stanford University, CA. The MPIQ (mean full-scale IQ of biological parents) was the primary determinant of the IQ of comparison siblings, and the quality of the home environment had an additional but small effect on verbal development. Using multiple regression analyses, cognitive outcome of girls with fragile X was correlated with the mean IQ of their parents, and to a lesser degree with the quality of home environment. FMR 1 protein % (FMRP) was correlated with girls' levels of distractibility. Girls with fragile X had higher IQs than boys, with relatively stronger Verbal Scales. The affected boys' Performance IQ was related to the mean parental IQ, while the boys' Full Scale IQ was correlated with FMRP %. The quality of boys' home environments affected their cognitive outcomes more so than in affected girls. (Dyer-Friedman J, Glaser B, Hessl D et al. Genetic and environmental influences on the cognitive outcomes of children with fragile X syndrome. J Am Acad Child Adolesc Psychiatry March 2002;41:237-244). (Respond: Dr Dyer-Friedman, Department of Psychiatry, Child Division, 401 Quarry Road, Stanford University School of Medicine, Stanford, CA 94305).

COMMENT. Both genetic/parental and environmental factors are significant in the prediction of cognitive outcome of children with fragile X syndrome. The specific factors influencing IQ are different in girls and boys.

Brain anatomy in fragile X syndrome. MRI scans and cognitive testing were performed in 37 children and adolescents with fragile X syndrome at Stanford University. Decreases in grey matter and increases in white matter were age- and gender-related. Caudate and ventricular CSF volumes were significantly enlarged, and caudate volumes decreased with age. IQ scores and volumes of cortical and subcortical grey matter were not significantly correlated, but were different from the correlations observed in normal children. (Eliez S, et al. Brain 2001;124:1610-1618).

PERINATAL DISORDERS

SEIZURE-ASSOCIATED BRAIN INJURY IN PERINATAL ASPHYXIA

Brain injury in term infants with neonatal asphyxia and seizures was evaluated by MRI and MRS at the University of California, San Francisco. Seizure severity was scored by seizure frequency and duration, EEG, and anticonvulsant therapy. Impairment of cerebral metabolism and neuronal integrity in the intervascular boundary zone and basal nuclei were measured by lactate/choline and N-acetyl aspartate/choline. Clinical seizures occurred in 37% of 90 infants studied. At 6 days of age (range, 1-13 days), seizure severity was associated with increased lactate/choline in both brain locations tested, and a diminished N-acetylaspartate/choline in the intervascular boundary zone but not in basal ganglia. The severity of seizures was independently associated with chemical evidence of brain injury and was not limited to the structural brain damage detected by MRI. (Miller SP, Weiss J, Barnwell A et al. Seizure-associated brain injury in term newborns with perinatal asphyxia. Neurology February (2 of 2) 2002;58:542-548). (Reprints: Dr AJ Barkovich, Department of Radiology, University of

California, 505 Parnassus Ave, San Francisco, CA 94143).

COMMENT. Seizure severity in term newborns with perinatal asphyxia can be associated with cerebral metabolic dysfunction and neuronal injury, independent of the structural damage detected by MRI. Previous studies using proton magnetic resonance spectroscopy have demonstrated that abnormalities of lactate and N-acetylaspartate in newborns with perinatal asphyxia are risk factors for abnormal neurodevelopmental outcome (Ashwal et al. Ann Neurol 1997;41:470-481).

Brain damage markers. The release of glial protein S-100B from astrocytes into the peripheral circulation, due to abnormal membrane integrity, is used as a measure of brain damage. In patients with head trauma, the higher the S-100B serum concentration, the more severe the outcome and neurologic impairment. Other proteins used as markers of brain damage include glial fibrillary acidic protein (GFAP) and neuron-specific enolase (NSE). In the past, most of the studies involved measurement of serum S-100 after pediatric cardiac operations. Leviton A and Dammann O (Acta Paediatr 2002;91:9-13) advocate the use of these protein markers in addition to serum inflammatory cytokines in the evaluation of newborns at risk for brain damage. Blood lactate as a measure of tissue anoxia in neonates has limitations (Saugstad OD. Acta Paediatr 2002;91:17-19).

PERINATAL AND CHILDHOOD STROKE

The epidemiology, risk factors, outcome and prognosis of perinatal and childhood stroke were reviewed at a workshop sponsored by the National Institute of Neurological Disorders and Stroke in Bethesda, MD, on Sept 18 and 19, 2000. *Neonatal stroke* occurs in approximately 1/4000 live births per year. Cause is often undetermined, but includes cardiac disorders, infection, blood abnormalities, and <5% associated with birth asphyxia. Coagulation disorders (factor V Leiden and prothrombin mutation, protein C, protein S, and antithrombin III deficiences are identified in 50% of infants and children with cerebral thromboembolism. Maternal factors may also contribute. An abnormal EEG during the first week after stroke is predictive of hemiplegia. Infarction demonstrated by neuroimaging and involving the internal capsule also predicts development of hemiplegia, whereas involvement of other regions is less predictive.

Childhood stroke incidence is estimated at 2-3/100,000 in the USA, and the US mortality rate attributed to stroke in children is 0.6/100,000. Stroke mortality has ranged from 7% to 28%. Causes include thromboembolism, arteriopathy, or are undetermined. Risk factors include cardiac disorders, coagulation disorders, sickle cell disease, infection, moyamoya, and arterial dissection. Up to 30% have postvaricella angiopathy. *Sinus venous thrombosis* occurs usually in the first year of life, and presents with focal abnormalities and seizures. Risk factors include head and neck infections, dehyration, perinatal complications, and coagulation disorders. *Hemorrhagic stroke* is less common than ischemic stroke in children. Risk factors include vascular malformation, malignancy, trauma, and coagulation disorders; AVM is the most common cause. The evaluation of stroke in children should include hematologic, metabolic, and angiographic studies. The Canadian Pediatric Stroke Registry (CPISR) outcome data, which includes 402 children with arterial ischemic stroke and 160 with sinus thrombosis, show that 27% are neurologically normal, 61% abnormal, 22% recurred, and a mortality of 12%. (Lynch JK, Hirtz DG, DeVeber G, Nelson KB. Report of the National Institute of Neurological Disorders and Stroke workshop on perinatal and childhood stroke.