FRAGILE X SYNDROME

Japanese patients with infantile autism were studied cytogenetically for the occurrence of fragile X (fra(x)) syndrome at the Universities of Kurume and Nagasaki. Fra(X) chromosome was detected in 2 (siblings) of 39 boys and in none of 8 girls; a frequency of 2.6% (1/38) in the study population of male autistic children. (Matsuishi T et al. Fragile X syndrome in Japanese patients with infantile autism. Pediatr Neurol 1987: 3: 284-7).

COMMENT. The fragile X syndrome is the most common familial form of mental retardation known, with an incidence of 1 in 1000 in the general population. The classical physical features in males are a long narrow face, large ears, and large testes. The pediatric neurologist may encounter cases referred because of large head circumference, hyperactive behavior and short attention span (ADD), and hand-flapping movement disorders. Poor eye contact and stereotyped movement have led to confusion with autism, reported in 5-53% of males with fragile X syndrome, and the classical manifestations have matched the DSM III diagnostic criteria for autism in some, as in the above study. For a comprehensive current overview of fragile C syndrome, see Hagerman RJ. Curr Probl Pediatr 1987;17:621-674.

VALPROATE-INDUCED MALFORMATIONS

Two children born with birth defects after intrauterine exposure to valproic acid are reported from the Dept Pediatrics Hopital Sainte-Justine, University of Montreal, Quebec, Canada. The drug was taken by the mothers throughout pregnancy as monotherapy for primary generalized epilepsy. One baby had facial dysmorphism, hypertelorism, anti-mongoloid palpebral fissures, a naevus flammeus on the forehead, portwine palpebral and nasal angiomas, arachnodactyly, triphalangeal thumbs, syndactyly, and a septum pellucidum cyst and dilated veluticles on CT scan. The second baby had facial dysmorphism, laryngeal hypoplasia, tracheomalacia, aberrant innominate artery and hydronephrosis. The authors concluded that valproic acid has probable teratogenic potential in humans but the spectrum of anomalies is broad and a definite fetal valproate syndrome is difficult to delineate. (Huot C et al. Congenital malformations associated with maternal use of valproic acid. Can J Neurol Sci 1987;14:290-293).

Comment. Approximately 50 malformed babies born to epileptic mothers taking valproate monotherapy have been reported. Contrary to the above opinion, Diliberti et al (Amer J Med Genetics 1984;19:473-481) have recognized a "fetal valproate syndrome", and the frequency of reports of valproate-induced congenital malformations together with other side-effects (liver failure, pancreatitis, endocrine abnormalities, weight gain) tend to contraindicate its use in pregnancy.

Portwine angioma noted in the first baby in this study of valproic acid toxicity may also be induced by thalidomide and alcohol ingestion during pregnancy (Jones et al. Lancet 1974;1:1076. Colver GB, Savin JA. Editorial. J Roy Soc Med 1987; 80:603). Dilated ventricles, defined by CT in the first baby, are reported as a reversible cerebral pseudoatrophy for the first time as a side-effect of valproic acid monotherapy in a 17-year-old with epilepsy (McLachlan RS. Can J Neurol Sci 1987;14:294).

For an update of antiepileptic drugs and teratogenicity, refer to Weber M. Rev Neurol (Paris) 1987;143:413. According to this report, the frequency of congenital malformations among children of epileptic mothers is twice that in the general population, genetic factors play a major role, and generally the teratogenic potential of antiepileptic drugs is low and does not contraindicate pregnancy in epileptic women. Many neurologists and certainly geneticists would advise stricter selectivity and caution in the choice of anticonvulsant for epileptic women contemplating pregnancy. Drugs with especially high or relatively frequent tetratogenic potential (e.g. trimethadione, phenytoin) are usually contraindicated, those with moderate or unknown degrees of propensity (primidone, valproic acid, carbamazepine, clonazapam) are avoided when possible, and the drug of choice, least likely to induce malformations and most often recommended, is probably phenobarbital.

CONGENITAL MALFORMATION AND MATERNAL PHENYLKETONURIA

Infants born to women with PKU are frequently mentally retarded, microcephalic, of low birthweight, and have various malformations. The results of an international collaborative study (in UK, Europe, Australia) by the MRC/DHSS Phenylketonuria Register concerning the diet of pregnant women with PKU are reported from the Institute of Child Health, London: (1) Normal birth weights and head circumferences and no malformations in 17 infants whose mothers received a strict low phenylalanine diet at conception; (2) below average birthweights and head circumferences and excess malformations a) in 29 infants whose mothers were on a relaxed or normal diet at conception and a strict diet during pregnancy, and b) in 18 infants whose mothers received no dietary treatment during pregnancy. Birth weights and head circumferences of the 64 infants were inversely related to the maternal phenylalanine concentrations at conception, and hyperphenylalaninemia in early gestation had a dose-dependent effect on the fetus. The authors estimate 2000 women with PKU of fertile age by 1990 in the UK and unless monitored closely through their reproductive lives, a substantial number of microcephalic and mentally retarded children will be expected. (Drogari E, Smith I (for correspondence), Beasley M, Lloyd JK. Timing of strict diet in relation to fetal damage in maternal phenylketonuria. Lancet 1987:2;927-930).

COMMENT. A National Collaborative Study of Maternal PKU was initiated in the US in 1984 and initial findings will be evaluated in 1991. Female PKU patients of fertile age receive education concerning risks to offspring and need for dietary and blood phenylalanine monitoring during pregnancies (O'Flynn M, Director PKU Clinic, Children's Memorial Hospital, Chicago, personal communication).

Levy HL and Waisbren SE (N Engl J Med 1983;309:1269) studied the effects of maternal PKU and hyperphenylalaninemia on 53 offspring from untreated pregnancies. Decreases in IQ, head circumference, and birth weight of the infants were correlated directly with the maternal IQ and inversely with maternal blood phenylalanine level. These authors concluded that maternal PKU has a substantial adverse effect on the fetus, and less severe maternal PKU may have subtle effects, resulting in slight reduction in IQ and intrauterine head growth. The UK report demonstrates that mothers with PKU who start a low phenylalanine diet before conception can give birth to normal infants despite variable phenylalanine blood levels during pregnancy. Congenital malformations