HEREDO-DEVELOPMENTAL DISORDERS

RETT SYNDROME FEMALE PHENOTYPES

The developmental data and spectrum of phenotypes in 120 females with Rett syndrome diagnosed with mutations in the MECP2 gene were evaluated at Gottingen University, Germany. The occipito-frontal head circumference (OFC) at birth was smaller in Rett (RTT) females than the normal population (P=0.000025). The median OFC was at the 30th percentile, 3 were <3rd %, and one >97th. The birth length and weight were also less than normal (P=0.000018 and P=0.00001, respectively); the median length and weight were at the 30th %. At the time of diagnosis, 46% had a height <3rd %, and 40% presented with microcephaly (OFC <3rd %). In development, 90% sat at 6-30 months of age (median 8 months), 45% never learned to walk, 33% never spoke and those who developed speech lost the ability at a median of 24 months (range 12-54 months). Hand function was lost at a median age of 18 months (range 8-75 months). Hand stereotypes developed in 96%, the median age at onset 24 months (range 6-116 months). Epilepsy was present at diagnosis in 69%, and the youngest age at onset was 6 months. Girls who never learned to walk had an early loss of language (P=0.001) and hand function (P=0.0002). Children with early regression are less likely to walk. Loss of hand function or language rarely occurs after 4 years of age. No patient with retarded development learned to sit after reaching age 30 months, walk after 48 months and speak after age 36 months, despite receiving therapy. Genetic testing has broadened the spectrum of phenotypes seen in RTT females. Mild or forme fruste variants can now be recognized, and unusual cases with precocious puberty or congenital varieties. (Huppke P, Held M, Laccone F, Hanefeld F. The spectrum of phenotypes in females with Rett syndrome. Brain Dev August 2003;25:346-351). (Peter Huppke MD, Neuropediatric Department, Abteilung Kinderheilkunde, Georg-August-Universitat Gottingen, Robert Koch Strasse 40 37075, Gottingen, Germany).

COMMENT. The early recognition of Rett syndrome by genetic testing facilitates counseling and interventional therapy. The finding that some signs of regression such as loss of hand function or language rarely occur in children with RTT after reaching 4 years of age may be consoling to parents, but the poor prognosis that follows a failure to sit, walk, or speak by ages 30 to 48 months may discourage further therapies and cause parental frustration.

Reduced folate transport to the CNS in Rett patients was studied in four female patients at University Hospital Aachen, Germany (Ramaekers VT et al. Neurology August (2 of 2) 2003;61:506-515). Two patients without and 2 with mutations of the MECP2 gene had normal values for red blood cell folate, serum folate, homocysteine, and methionine. CSF of all four had low 5-methyltetrahydrofolate (5MTHF), neopterin, and the serotonin end-metabolite 5-HIAA, and the total folate binding capacity was lowered. Treatment with oral folinic acid normalized 5-MHTF and 5-HIAA levels in CSF, and resulted in partial clinical improvement. Clinical trials of folinic acid in Rett patients at an early pre-regression age may be justified.