

NEURO CUTANEOUS SYNDROMES

CORTICAL MALFORMATIONS IN NEUROFIBROMATOSIS TYPE 1

Different types of malformations of cortical development in three cases of neurofibromatosis 1 (NF1) are reported from the University of Siena, Italy. Patient 1, a 3-year-old boy with infantile spasms, café-au-lait spots, Lisch nodules, and skin fibromas had an abnormal MRI with a large dysplasia involving the right temporoinsuloparieto-occipital cortex. Patient 2, a 19-year-old woman with a history of infantile spasms, café-au-lait spots, Lisch nodules, axillary and inguinal freckles, and neurofibromas had an MRI showing a periventricular band of heterotopic gray matter and overlying pachygyric cerebral cortex. Patient 3, an 18-year-old man with mental retardation, infantile febrile seizures, left partial clonic and generalized seizures at age 8 years, EEG paroxysmal activity on the left temporal area, had an MRI showing a left perisylvian polymicrogyria. Neurofibromin may play a role during several stages of cortical development. (Balestri P, Vivarelli R, Grosso S et al. Malformations of cortical development in neurofibromatosis type 1. *Neurology* December (2 of 2) 2003;61:1799-1801). (Reprints: Dr Paolo Balestri, Department of Clinical Pediatrics, University of Siena, Viale M Bracci, Le Scotte, 53100 Siena, Italy).

COMMENT. Severe cortical malformations are considered rare in NF1. When present they can be extremely variable and complex, and are associated with drug resistant epilepsy and mental retardation. According to the Barkovich classification, cited by the authors (Barkovich AJ et al. *Neurology* 2001;57:2168-2178), the first patient reported above had a malformation showing abnormal neuronal and glial proliferation or apoptosis. The abnormality in the second patient could be related to abnormal neuronal migration, and the third is an example of an anomaly caused by defective cortical organization. These malformations represent different stages of cortical development, all resulting from deficiencies of neurofibromin.

Malformations of cortical development (MCD) in epilepsy are reviewed from the Institute of Neurology, Queen Square, London (Sisodiya SM. *Lancet Neurology* January 2004;3:29-38). The most common MCDs include focal cortical dysplasias, periventricular heterotopia, polymicrogyria, band heterotopia, lissencephaly, dysembryoplastic neuroepithelial tumors, and microdysgenesis. Subtle MCD not detectable on MRI and identified in surgical tissue samples may sometimes underlie epilepsies termed cryptogenic.

COGNITIVE AND FINE MOTOR DEFICITS AND MRI HYPERINTENSITIES IN NEUROFIBROMATOSIS TYPE 1

The relationship between cognitive impairment, fine motor deficits, and T2-weighted MRI intensities in neurofibromatosis type 1 (NF1) was investigated in 100 patients and 100 healthy controls in a study at University Hospital of Munster, Germany. T2 hyperintensities (T2H) were found in 66% of 56 patients younger than 16 and in 48% of 44 patients older than 16. As a group, patients with NF1 had normal scores on the WISC-R and WAIS-R. Patients with normal MRI had close to the mean IQ of the normal population whereas those

who showed T2H (n=58) had significantly depressed verbal, performance, and full-scale IQ scores. On a test of fine motor skills, patients with T2H on MRI showed lower scores than those with normal MRI. Cognitive and motor performances of patients with T2H were not significantly correlated with the number of cerebral regions affected by T2H. Foci of T2H affected a single cerebral region in 40% of patients with T2H, 2 or 3 regions in 48%, and 12% had 4 or more regions affected. Hyperintensities on T2-weighted MRI represent a biological marker for impaired cognitive and fine motor performance in patients with NF1. (Feldmann R, Denecke J, Grenzebach M et al. Neurofibromatosis type 1. Motor and cognitive function and T2-weighted MRI intensities. **Neurology** December (2 of 2) 2003;61:1725-1728). (Reprints: Dr R Feldmann, Department of Pediatrics, University of Munster, Albert-Schweitzer St, 33, D-48129 Munster, Germany).

COMMENT. This study demonstrates a strong relation between cognitive and fine motor performance and the presence of T2 hyperintensities on the MRI of patients with NF1. The number of cerebral regions affected by T2H is not correlated with cognitive and motor performances. Previous reports have shown variable results. In a study of 12 families reported from Johns Hopkins Hospital, Baltimore, children with NF1 compared to unaffected siblings had a lower IQ, multifocal cognitive deficits, and reading and neuromotor disabilities. In this study, cognitive differences correlated with the number of MRI "unidentified bright objects" (T2H). (Hofman KJ, Denckla MB et al. **J Pediatr** 1994;124:S1-S8). Patients identified with T2H should be considered for special education services.

FUNCTION OF TUBERIN AND HAMARTIN IN TUBEROUS SCLEROSIS PATHOGENESIS

The genetics and function of tuberin and hamartin in the pathogenesis of tuberous sclerosis complex (TS) are reviewed in a presentation at a "Festschrift" honoring Dr Michael J Painter of the Division of Pediatric Neurology, Children's Hospital of Pittsburgh, PA. The prevalence of TS is 1/10,000, two-thirds being sporadic. Among familial cases, half are linked to chromosome 9q34 (TSC1) locus and half to the 16p13.3 (TSC2) locus. Most sporadic cases are due to defects in TSC2. The TSC1 gene encodes the protein, hamartin, and the TSC2 gene encodes tuberin. The gene for polycystic kidney disease is located centromeric to TSC2, accounting for the occurrence of both conditions in families with contiguous gene syndromes. Tuberin and hamartin function as tumor suppressors, inhibiting the activity of rapamycin (mTOR) and regulating cell growth. (Narayanan V. Tuberous sclerosis complex: genetics to pathogenesis. **Pediatr Neurol** Nov 2003;29:404-409). (Respond: Dr Narayanan, Barrow Neurological Institute, St Joseph's Hospital and Medical Center, 500 W Thomas Rd, Suite 930, Phoenix, AZ 85013).

COMMENT. It is suggested that knowledge of the cellular functions of tuberin and hamartin might lead to new drugs that modulate signaling pathways. These could be effective in the control of epilepsy and cognitive impairment associated with TS. The discovery of tumor suppressor genes has provided insight into genetic alterations that contribute to neoplasia. These genes contribute to tumorigenesis only when both alleles have been inactivated. (Charrow J. In: **Progress in Pediatric Neurology III**, PNB Publ, 1997;Chpt 10:435-439).