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CNS NEOPLASMS

NF1-ASSOCIATED ASTROCYTOMAS

Nine symptomatic NF1-associated juvenile pilocytic astrocytomas (JPA) were examined for cancer-related gene products in a study using immunohistochemistry and Western blots at Washington University School of Medicine, St Louis, MO; and the Mayo Clinic, Rochester, MN. NF-1 associated JPA strongly expressed the antibody epitope PEN5, a marker of post-O2A stage oligodendroglial cells, and showed no alterations in the protein expression profiles p53, p16, retinoblastoma (RB), epidermal growth factor receptor (EGFR), cyclin-dependent kinase 4 (CDK4), platelet-derived growth factor A (PDGF-A), and PDGF-Ra. The study supports a distinct molecular pathogenesis for NF1-associated JPA, which differs from the genetic changes seen with the more clinically aggressive and diffusely infiltrative, sporadic fibrillary astrocytomas. (Li J, Perry A, James CD, Gutmann DH. Cancer-related gene expression profiles in NF1-associated pilocytic astrocytomas. Neurology April (1 of 2) 2001;56:885-890). (Reprints: Dr David H Gutmann, Department of Neurology, Washington University School of Medicine, Box 8111, 660 S Euclid Avenue, St Louis, MO 63110).

COMMENT. Grade I juvenile pilocytic astrocytoma (JPA) develops in 15% of children with neurofibromatosis 1 (NF1). The incidence of malignant progression in JPA is much lower than with sporadic fibrillary astrocytomas. The mean age at diagnosis of JPA is 4.5 years. Most are clinically benign, but some progress and cause visual loss and hypothalamic dysfunction. The above study attempts to explain why benign astrocytomas become malignant in NF1, a question further discussed in an editorial (Ruggieri M, Packer RJ. Neurology 2001;56:827-829).

Neurofibromin, the NF1 gene product, acts as a tumor suppressor protein. Mutation in the NF1 gene is associated with inadequate levels of neurofibromin, leading to increased cell proliferation. In NF1, tumors develop in patients with an additional mutation and a loss of heterozygosity. By studying proteins with expression profiles typical of fibrillary astrocytomas, Li and associates show that NF1-associated JPA tumors differ from their sporadic counterpart by exhibiting loss of neurofibromin expression, and demonstrate that gene expression profile

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abnormalities found in fibrillary astrocytomas are lacking in JPA. It is suggested that distinct genetic pathways in NF1 may produce subsets of astrocytomas.

Dysplastic and heterotopic neurons in focal cortical dysplasia. These cell types were differentiated by demonstrating a differential expression of glutamate and GABA-A receptor subunit mRNA in single immuno-histochemically labeled neurons, microdissected from human focal cortical dysplasia specimens removed during epilepsy surgery, at the Children's Hospital of Philadelphia, PA (Crino PB et al. Neurology 2001;56:906-913). Dysplastic and heterotopic neurons may be pharmacologically distinct and differ in their contribution to epileptogenesis in focal cortical dysplasia.

SEIZURE DISORDERS

GENETIC BASIS OF CARBAMAZEPINE HYPERSENSITIVITY

The genetic basis of carbamazepine hypersensitivity was investigated in 60 affected patients (37 with mild rashes and 23 severe reactions) and 63 control non-sensitive subjects taking carbamazepine and treated at the University of Liverpool, UK. Using PCR and focusing on the major histocompatibility complex (MHC) on chromosome 6, a region linked to diseases of immune etiology, the association of hypersensitivity with polymorphisms in the TNFa promotor region gene and with HLA-DR3 and -DQ2 was determined. The TNF2 allele acted as a predisposing factor for CBZ sensitivity, but only in severe reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Also, HLA-DR3 and -DQ2 were associated with severe reactions. None of the alleles were independently associated with CBZ sensitivity. Hypersecretion of TNFa (tumor necrosis factor a) may determine the severity of the tissue reaction to CBZ. (Pirmohamed M, Lin K, Chadwick D, Park BK. TNFa promotor region gene polymorphisms in carbamazepine-hypersensitive patients. Neurology April (1 of 2) 2001;56:890-896). (Reprints: Dr M Pirmohamed, Department of Pharmacology and Therapeutics, University of Liverpool, Ashton Street, Liverpool, L69 3GE, UK).

COMMENT. CBZ hypersensitivity reaction, an immune mediated side effect of anticonvulsant treatment, is found to have a genetic basis involving polymorphisms and hypersecretion of tumor necrosis factor a (TNFa) contained within the major histocompatibility complex on chromosome 6. Further studies may help to identify susceptible patients and iessen the risk of these serious skin reactions.

COGNITIVE EFFECTS OF CARBAMAZEPINE AND LAMOTRIGINE

The cognitive and behavioral effects of carbamazepine (CBZ) and lamotrigine (LTG) were assessed and compared in 25 healthy adult volunteers, using a double-blind, randomized crossover design with two 10-week treatment periods, at the Medical College of Georgia, Augusta, and New York University, New York. A neuropsychological test battery was administered at the end of each AED treatment period (CBZ mean dose 696 mg/day, and LMG 150 mg/day), at pretreatment baselines, and at 1 month after completion of the last AED treatment. Comparison of the two AEDs showed better cognitive and subjective behavioral measures for LMG than CBZ. Measures included cognitive speed, memory, graphomotor coding, neurotoxic symptoms, mood, sedation, and perception of cognitive performance. Compared to nondrug periods, performance on CBZ was