No evidence for the involvement of interleukin 2 or the immunoglobulin heavy chain gene cluster in determining genetic susceptibility to multiple sclerosis

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LETTERS TO THE EDITOR

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Here we report the investigation of two promising candidate multiple sclerosis susceptibility genes. Each is biologically plausible, having a function suggesting possible involvement in the pathogenesis of the disease and positional, having existing linkage evidence supporting its candidacy. The two differ, however, in the origin of the supporting linkage evidence. This comes mainly from the analysis of animal models in the case of interleukin 2 (IL-2) and from human studies in the case of the immunoglobulin heavy chain gene cluster.

Interleukin 2 is a cytokine intimately involved with both the function and regulation of the immune system. It has both proinflammatory and anti-inflammatory actions, promoting T cell proliferation during cell mediated immune responses and, conversely, being crucial both for the development and maintenance of self tolerance. Genetic analysis of experimental autoimmune encephalomyelitis (EAE) provides strong evidence supporting the candidacy of IL-2 as a susceptibility gene.

The immunoglobulin heavy chain gene cluster is another highly promising candidate. Plasma cells and B lymphocytes are readily detected in areas of acute demyelination and the occurrence of oligoclonal immunoglobulin bands in the spinal fluid of affected people is a distinctive feature of the disease. Moreover, the cluster is encoded towards the telomere of the immunoglobulin heavy chain gene cluster.

To investigate its role as a susceptibility factor in multiple sclerosis, we typed a closely encoded microsatellite marker in 502 trio families (both parents and a single affected offspring). Transmission disequilibrium testing (TDT) of these data disclosed no significant evidence for linkage disequilibrium (table). The expression of IL-2 is under the control of transcription factor 8 (TCFP8), the gene for which is encoded on chromosome 10p11.

We typed three microsatellite markers encoded within the immunoglobulin heavy chain gene cluster in 460 simplex families. Once again TDT failed to show evidence for linkage disequilibrium (table) at any of these markers. As the markers are encoded within a 200 kb region, we also subjected them to multipoint TDT analysis but no haplotypes showing significant transmission distortion were found.

These results suggest that neither of the tested candidates has any major effect in determining genetic susceptibility to multiple sclerosis. However, in considering these data it is important to remember that the negative results could represent a type II error as, even with the large numbers of simplex families used, the power of this type of candidate gene study is limited when the effects attributable to the susceptibility genes are modest. A further possibility is that the available evidence for linkage is falsely positive and that, in fact, no susceptibility genes are encoded in these regions. The low score observed in the immunoglobulin heavy chain gene cluster region is significantly short of the 5% genomewide significance threshold suggested by Lander and Kruglyak (lod score = 4.0). A third possibility is that the linkages are genuine but unrelated to the candidates we have tested. We favour this explanation with the available data suggesting that alternative candidates from these regions are responsible for the observed linkages.

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ALASTAIR COMPSTON

Coma in a patient with Alzheimer's disease taking low dose trazodone and ginkgo biloba

We describe a patient with Alzheimer's disease who developed coma a few days after starting low dose trazodone associated with ginkgo biloba. Coma was reversed by flumazenil, a specific antagonist of the benzodiazepine (BDZ) receptor. The finding is relevant in that, although the sedative effects of trazodone are well known, the drug is inactive on the BDZ receptor. On the other hand, ginkgo is active on the receptor, but sedation has so far never been reported.

In March 1999, an 80 year old woman was first evaluated in our facility and given a diagnosis of probable Alzheimer's disease (NINCDS-ADRDA criteria) of a moderate severity (mini mental state examination of 10/30). She had no physical comorbidity or vascular risk factors. At the time of observation she was taking 3.5 mg bromazepam for mild restlessness, anxiety, and irritability, with only partial benefit (neuropsychiatric inventory: anxiety 4/12, irritability/lability 3/12). A dose of 5 mg donepezil at bedtime was added with the aim of improving both cognitive function and behaviour, together with 600 mg vitamin E twice daily.

After 3 months, no improvement of cognitive function, behaviour, or daily function could be detected. Donepezil was discontinued and vitamin E was also discontinued, with the development of echomimetic bruises on all limbs. Ginkgo biloba ((Egb 761) 80 mg) twice daily was added. Rivastigmine was not considered a feasible option because it was not possible to have frequent clinical follow up visits during the titration phase. For a better control of behavioural disturbances, bromazepam was replaced with 20 mg trazodone twice daily.

The day after the visit, the new therapeutic regimen was initiated. Sedation or other adverse effects did not appear, and the care giver reported improvement of anxiety. On the next day, the improvement of behavioural disturbances was sustained, still in the absence of sedation. At 600 pm of the third day, the patient developed instability of gait and drowsiness. At 700 pm she fell asleep. The care giver tried to wake her by slapping her face, but without success. Overall, she had taken 100 mg trazodone and 320 mg Egb 761 in about 50 hours. A physician on call found that blood pressure was 120/55 mm Hg and her Glasgow coma scale was 6/15. The patient was taken to the nearest hospital.