LETTERS TO THE EDITOR

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

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 a patient with multiple sclerosis indicates that these regions are responsible for the observed linkages.  

We thank J Deans and M Fraser for help with the collection of samples and the members of the Associated British Neurologists for notifying us of multiple sclerosis cases. Financial support was provided by the Multiple Sclerosis Society of Great Britain and Ireland, the Medical Research Council, and the Wellcome Trust.

ROBERT FEAKES
STEPHEN SAWER
BELINDA SMILLIE
JEFF CHATAWAY
SIMON BROADLEY
ALASTAIR COMPTON
University of Cambridge Neurology unit,
Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QQ, UK

DAVID CLAYTON
MRC Bioinformatics Unit, Institute of Public Health,
University Forsey Site, Robinson Way, Cambridge, CB2 2SR, UK

ALASTAIR COMPTON

Coma in a patient with Alzheimer’s disease taking low dose trazadone and ginkgo biloba

We describe a patient with Alzheimer’s disease who developed coma a few days after starting low dose trazadone 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 trazadone 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, taking into account the development of echchimotic 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 and noticed, 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 trazadone 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.

Table 1 Transmission disequilibrium testing results

<table>
<thead>
<tr>
<th>Marker</th>
<th>Het</th>
<th>df</th>
<th>p Value</th>
<th>Primers</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL2</td>
<td>0.89</td>
<td>7.31</td>
<td>4</td>
<td>0.12</td>
</tr>
<tr>
<td>TCF8</td>
<td>0.73</td>
<td>0.08</td>
<td>2</td>
<td>0.96</td>
</tr>
<tr>
<td>D14S1419</td>
<td>0.56</td>
<td>2.31</td>
<td>3</td>
<td>0.51</td>
</tr>
<tr>
<td>D14S1420</td>
<td>0.67</td>
<td>0.74</td>
<td>2</td>
<td>0.69</td>
</tr>
<tr>
<td>D14S826</td>
<td>0.74</td>
<td>1.74</td>
<td>4</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Each microsatellite was amplified by PCR from genomic DNA with fluorescent labelling of the forward primer and genotyped using the Applied Biosystems GENESCAN/GENOTYPER system (primers as shown in table). TDT was performed using the TRANSMIT program version 1.1, considering only those alleles with a frequency of greater than 10% (corresponding to the number of degrees of freedom (df) in the table). The chromosome 14 markers are listed in map order.

The families were recruited from throughout the United Kingdom. All are white and the affected offspring meet the Poser criteria, 95% having clinically definite, category A or B, disease.


Ed Adrian Building, University Forsey Site, Robinson Way, Cambridge, CB2 2SR, UK

Correspondence to: Professor Alastair Compton
alastair.compton@medschl.cam.ac.uk