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 cerebrospinal fluid of affected patients is a distinctive feature of the disease. Moreover, the cluster is encoded towards the telomere of chromosome 14q where linkage evidence from the United Kingdom sibling pair families is at its strongest (lod score=3.0).

The gene for IL-2 is encoded on chromosome 4q26. 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 genetic control of transcription factor 8 (TCF8), the gene for which is encoded on chromosome 10p11. Because variation in IL-2 expression could contribute to susceptibility of multiple sclerosis, we also typed a microsatellite encoded close to the TCF8 gene in the same 502 families. Again, the TDT results (table) were negative.

We typed three microsatellite markers encoded within the immunoglobulin heavy chain gene cluster in 460 simplex families. Once again TDT failed to disclose 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 lack of linkage observed on the immunoglobulin heavy chain gene cluster region is significantly short of the 5% genomewide significance threshold suggested by Lander and Kruglyak (1). As 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.

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

ROBERT FEAKES
STEPHEN SAWCER
BELINDA SMILLIE
JEFFREY CHATAWAY
SIMON BROADLEY
ALASTAIR COMPSTON
University of Cambridge Neurology Unit,
Addenbrooke’s Hospital, Hills Road, Cambridge,
CB2 2QZ, UK

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

ALASTAIR COMPSTON

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>0.12</td>
<td>AAG GAC AGC TAC CAC TGG TTC CCC TCG CCG CCC</td>
</tr>
<tr>
<td>TCF8</td>
<td>0.73</td>
<td>0.08</td>
<td>0.96</td>
<td>AGA GGA TCC TGT TCA CTA CTT GAC CAG TGG</td>
</tr>
<tr>
<td>D14S1419</td>
<td>0.56</td>
<td>2.31</td>
<td>0.51</td>
<td>TAG GGA CAC GGA GTT CAC TTA CAT AAT TAA GAA</td>
</tr>
<tr>
<td>D14S1420</td>
<td>0.67</td>
<td>0.74</td>
<td>0.69</td>
<td>CAC TTA ATG TTA AAA TTA GAA CCC GAC</td>
</tr>
<tr>
<td>D14S826</td>
<td>0.74</td>
<td>1.74</td>
<td>0.78</td>
<td>TGG TTT AGG AGA GGA GCA GGT TGT TCT CTA GAG CTA TAA TAA CCC AG</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 2.5, 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.

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 2.5, 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.

where 1 mg flumazenil intravenously was administered. The patient awoke immediately.

Medicine bottles at the patient’s home were examined. The medications remaining in the containers were consistent with the prescribed doses, and medications other than those prescribed were not found anywhere in the house.

Trazodone and ginkgo were discontinued and bromazepam was resumed. The patient was re-evaluated 2 months later. Cognitive functions and behaviour were unchanged.

The pathogenesis of coma would have remained unexplained in this patient had not flumazenil been fortuitously administered. This led to an investigation of the links among trazodone, ginkgo, and the GABAergic system.

Ginkgo biloba is active on cognition in Alzheimer’s disease through its antioxidant properties. Flavonoids represent the major active component of the extract and possess properties. Flavonoids might have blocked the direct effect of flavonoids, thus causing GABAergic activity to fall below the threshold of clinical manifestation (figure).

Ginkgo is widely used and is thought to be a harmless food supplement. Although we warn that the adverse effects of the simultaneous administration of trazodone and ginkgo should be further confirmed, we think that natural compounds such as ginkgo can have, in some clinical circumstances, adverse effects of similar magnitude as traditional drugs.

2 Hamik A, Peroutka SJ. 1-(m-Chlorophenyl)piperazine (mCPP) interactions with neurotransmitter receptors in the human brain. Biol Psychiatry 1989;25:569–75.

Pathway from trazodone to coma.

Bickerstaff's brainstem encephalitis subsequently to Campylobacter jejuni enteritis

Bickerstaff's brainstem encephalitis (BBE) is characterised by acute ophaloplegia and ataxia preceded by infection. BBE rather than Miller Fisher syndrome is usually diagnosed for patients who show drowsiness and have brisk reflexes, extensor plantar responses, and long tract sensory disturbance. Bickerstaff and Closs speculated that the aetiology of BBE is similar to that of...
Guillain–Barré syndrome (GBS) because antifilaria and CSF albuminocytological dissociation was detected in one of their three patients. Because prior infection is frequent in BBE, as in GBS, autoimmune mechanisms produced by microbial infections may function in GBS. A review of the literature in English turned up eight cases of BBE in which the pathogens of antecedent infection had been identified. The reported antecedent infections in BBE are herpes simplex virus, cytomegalovirus, Epstein–Barr virus, varicella zoster virus, measles virus, Salmonella typhi, and Mycoplasma pneumoniae. We here describe a case of BBE who had a previous reported history of Campylobacter jejuni enteritis. A 17-year-old youth had fever and diarrhoea that cleared up over a period of 5 days. Eight days after the resolution of this illness, he experienced unsteady gait (day 1), and the next day he required assistance to walk and experienced vertigo. On day 3, he could no longer walk and vomited several times. He was apyrexic but drowsy. The pupils were normal and responded promptly to light. There was no limitation of ocular movement. There was no limitation of the right eye. Limb power was normal. Bifacial palsy was present, and the patient in our case responded favourably to light. There was no limitation of ocular movement, and the patient in our case responded favourably to light. There was no limitation of ocular movement. Limb power was normal. Bifacial palsy was present, and the patient had been immunised mice against C. jejuni. The specimen obtained from the patient was tested against C. jejuni lipopolysaccharide (LPS) using the enzyme immunoassay (EIA) assay. The O antigen of the strain OH 4384 was identified as being a mixture of O1 and O14 serogroups, and the patient was serologically and cerebrospinal fluid (CSF) antibody measurements. BBE and GBS was another possible diagnosis, and this had been reviewed elsewhere. The presence of BBE (or overlapping BBE and GBS) after infection by C. jejuni supports the speculation that BBE and GBS are closely related and that BBE is an autoimmune disorder that occurs after microbial infection.

We previously reported the occurrence of GBS in two family members after C. jejuni infection. The occurrence of the second case is very similar to those of the case reported here; the patient was comatose and showed external ophthalmoplegia. Overlapping GBS and BBE, therefore, could also be diagnosed for patients with Campylobacter-ganglioside serology testing was not possible because no serum was kept. Aspinall et al. proposed that the lipopolysaccharide of the strain OH 4384 isolated from the patient with GBS has a GT1a-like structure. We partially confirmed this using anti-GT1a monoclonal antibody but in addition showed that OH 4384 has lipopolysaccharides that bear GM1, GM2, GD1a, GT1b, or GQ1b epitopes. Gooyear et al. immunised mice with the lipopolysaccharide from OH 4384 and cloned three monoclonal antibodies with GQ1b reactivity. Anti-GQ1b IgG usually cross reacts with GT1a, and GQ1b is abundantly expressed in human ocular motor nerves. Infection by C. jejuni bearing a GT1a-like or GQ1b-like lipopolysaccharide may induce the production of anti-GT1a or GQ1b IgG antibody, which then may bind to ocular motor nerves causing paresis of the extracocular muscles in patients with overlapping BBE and GBS.

Effective therapy for BBE has yet to be established. As stated above, BBE and GBS are closely related; therefore, steroids should not be used to treat BBE. Instead, the established treatments for GBS, plasmapheresis and intravenous patient globulins (IVIg), should be used. Some patients with BBE have responded favourably to plasmapheresis, and the patient in our case responded favourably to IVIg. We recommend not giving steroids, but using plasmapheresis to treat BBE. Controlled clinical trials are required to establish the efficacy of these procedures as therapeutic for BBE.

This research was supported in part by grants-in-aid for Scientific Research (10780482 and 10557063 to NY) from the Ministry of Education, Science, Culture and Sports of Japan and from the Mitsubishi Foundation for Medical Research and a Research Grant for Neuroimmunological Diseases from the Ministry of Health and Welfare of Japan. We thank Dr Masaki Takahashi (Department of Microbiology, Tokyo Metropolitan Institute of Public Health) for the C. jejuni serotyping and Dr Michiaki Koga (Department of Neurology, Dokkyo University School of Medicine) for the anti-C. jejuni antibody measurements.

Nobuhiro Yuki, Masaaki Odaka, Koichi Hiraya

Department of Neurology, Dokkyo University School of Medicine, Kitahokuso 80, Tochigi 321-0293 Japan

Correspondence to: Dr N Yuki
yuuki@dokkyomed.ac.jp
Our patient had Hashimoto’s disease with a marked increase in antithyroid antibodies. Her thyroid function tests were normal on thyroid replacement therapy. Diffusely abnormal EEG and high CSF protein were found at her conclusion stage. Her encephalopathy markedly responded to steroid therapy. Other aetiologies such as infectious, metabolic, toxic, neoplastic, vascular, and paraneoplastic causes had been excluded. These findings are consistent with previously described cases of Hashimoto’s encephalopathy.

What is notable in our case is that the myelopathy developed 2 months before encephalopathy. Some diseases, including multiple sclerosis, scoliosis, and vascular accident, are known to cause myelopathy. The lack of typical findings of brain MRI and oligoclonal bands in CSF, and normal IgG index were not compatible with multiple sclerosis. Findings of myelography and spinal MRI suggested that myelopathy was not associated with sclerosis. Slow progression over a month and the distribution of sensorimotor disturbance were not compatible with vascular accident. We think that her myelopathy was also associated with Hashimoto’s disease because she subsequently had encephalopathy and other conditions which could cause myelopathy were excluded. This is the first case of myelopathy associated with Hashimoto’s disease.

The aetiology and the pathological basis of Hashimoto’s encephalopathy are not known. Brain et al.1 described localised cerebral oedema as a possible cause of Hashimoto’s encephalopathy. This hypothesis may be supported by reversible MRI abnormalities and excellent response to steroid therapy.1 Ishii et al.2 postulated that a toxic effect of TRH on the CNS had an important role in Hashimoto’s encephalopathy.

In our patient antithyroid antibodies were detectable not only in serum but also in CSF. Shaw et al.3 reported that antithyroid antibodies were detectable in CSF from one of four patients with Hashimoto’s encephalopathy. Marked higher titres of antithyroid antibodies in serum compared with those in CSF in our patient might suggest that antithyroid antibodies in CSF were mainly derived from plasma. Therefore, antithyroid antibodies in CSF might be a “litigation induced neurosis” still has some traumatic” or “postconcussion” syndrome is “to be treated with great caution”. However, this guide to the management of mild head injury begins in an admirable way by giving the incidence of this condition or of its complications should carry a health warning “to be treated with great caution”. However, this guide to the management of mild head injury begins in an admirable way by establishing carefully both the basis on which its statistics are derived and its authors’ own definition of what they mean by “mild head injury”. Thus the statistics and authors provide are likely to prove more reliable than most. Their careful studies indicate a probable incidence of 3% of persisting symptoms 28 days or more after mild head injury.

Although the view that the “posttraumatic” or “postconcussive” syndrome is a “litigation induced neurosis” still has some currency, particularly in legal circles, there are now sufficient pathological and imaging studies to agree a probable pathological basis for the syndrome. This volume sets out the evidence for such a case in a clear and lucid manner including some mention of the more recent MRI and SPECT evidence. Similarly, the more recent work undertaken by clinical psychologists carrying out detailed psychometric assessments of these patients has provided good support evidence for the reality of the continuing cognitive and performance problems that such patients have, often for prolonged periods after an apparently mild injury. The authors present a wealth of clinical and psychological data in a clear and lucid manner and the layout progresses naturally to

For those not versed in the history of this text, Douglas McAlpine, Nigel Compston, and Charles Lumsden, in 1955, authored its fore-runner Multiple Sclerosis. This was then succeeded by two editions of Multiple Sclerosis: a Reappraisal with the addition of E D Acheson to the authorship. The first edition of its offspring McAlpine's Multiple Sclerosis appeared in 1985. This current edition is inextricably linked to its past; its principal author, Alastair Compston, being the son of Nigel to whom the book is dedicated. Bryan Matthews, a current contributor, was the main author of the first edition.

Enough of the history, what of the book? As internationally recognised experts in their specific areas of multiple sclerosis, the present group of authors requires no introduction. The book contents have changed considerably since I first acquired the 1965 edition that concentrated on epidemiology (including a fold away map), clinical studies, and chemical pathology. The present text, lavishly illustrated, contains a balance of genetics, neurobiology, and pathophysiology as well as maintaining, for the generalist, authoritative sections on epidemiology, clinical presentation, diagnostic methods, treatment, and management.

Alastair Compston's initial chapter, itself a literary gem, elegantly sets the scene, outlining the early clinical and pathological descriptions of disease as well as the experiences of sufferers from the worlds of medicine and the arts. He goes on, in subsequent chapters, to discuss epidemiology, pathogenesis, and treatment. In relation to treatment he comprehensively reviews the evidence for disease modifying therapies and, with the aid of a particularly memorable figure (14.8), addresses the symptomatic treatments available for both early and late disease. Bryan Matthews reviews the symptoms and signs of multiple sclerosis and its differential diagnosis. As would be expected, from his vast experience and clarity of writing, these sections are of great practical value—for example, the description of the warning signs (red flags) that should lead to diagnostic caution. Ian McDonald addresses imaging and other diagnostic techniques as well as pathophysiology of disease. These chapters reflect his own career at the forefront of electrophysiological investigations and thereafter the recognition and development of the potential of MRI, both diagnostically and in the understanding of disease mechanisms. George Ebers writes on the natural history, drawing on the literature and his own seminal work with Brian Weinshenker. Finally, and perhaps for the clinician most impressively, Hans Lassman and Hartmut Wekerle describe the immunology and current state of experimental models with great clarity. I am reminded, when praising a book so fully, of the dangers of sycophancy. Indeed, as Groucho Marx once wrote to an author pleased with his review “I am delighted that you are delighted that I am delighted”. Of course, there are omissions, the authors accept that while trying to be comprehensive they have delved into their specific areas of interest. With increasing specialisation in multiple sclerosis care within the United Kingdom, there is disappointingly nothing on how to develop a service and only a page on rehabilitation and the role of therapists (although evidence based medicine possibly justifies no more). There is also no mention of the economic burden of disease or the cost benefit and cost utility of available treatments and multiple sclerosis services.

These are, however, minor criticisms and the authors must be warmly congratulated on producing an outstanding reference text that Nigel Compston and his original coauthors would be immensely proud of, their intention at the outset being that of stimulating interest “in the ever widening field of demyelinating disease”. This book clearly fulfills that legacy and definitively presents the current state of knowledge. In their preface, the authors state that the final solution to the problems of multiple sclerosis, in particular more effective treatments, must await another edition (or more). Indeed, Dan Quayle might well have been referring to multiple sclerosis when he famously once said, “there are a lot of uncharted waters still out there in space”.

DAVID HARDY


Advances and Technical Standards in Neurosurgery was created in 1974 as an adjuvant to the European postgraduate training system for young neurosurgeons. It has also proved popular with accredited neurosurgeons wishing to keep up to date with recent developments in the field. The first half of each volume reviews topics in which important advances have been made, and this is followed by in depth reviews of topical subjects from experienced clinicians.

The advances section begins with a review from Lausanne of the delivery of neuroactive substances to the CNS using the technique of encapsulation of xenogenic cells to avoid the problems of immune rejection. Possible applications in pain relief and amytrophic lateral sclerosis are discussed. Fries and Pernecky then present the Mainz experience with rigid endoscopes, both for conventional procedures such as third ventriculostomy, cyst drainage, and tumour biopsy, and then discuss newer applications such as endoscope assisted microneurosurgery of aneurysms, tumours, and as an aid to microvascular decompression of cranial nerves in the posterior fossa. The final chapter in the first section presents the history and technique of chronic deep brain stimulation for movement disorders, reviews the results from Grenoble, Lille, and Creteil, and compares the outcomes with ablative surgery and neural transplantation. In the technical standards section there are reviews of recent advances in the treatment of CNS germ cell tumours, the surgery of hypothalamic gliomas, and approaches to the anterior cranial fossa with preservation of olfaction.

The quality of reviews in this book is excellent. Each is by a renowned expert in the field, and is well referenced for further reading. Those not already familiar with this series will find it both informative and thought provoking.

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

ROBERT FEAKES, STEPHEN SAWCER, BELINDA SMILLIE, JEREMY CHATAWAY, SIMON BROADLEY, ALASTAIR COMPSTON, DAVID CLAYTON and ALASTAIR COMPSTON

*J Neurol Neurosurg Psychiatry* 2000 68: 679
doi: 10.1136/jnnp.68.5.679

Updated information and services can be found at:
[http://jnnp.bmj.com/content/68/5/679.1](http://jnnp.bmj.com/content/68/5/679.1)

These include:

**References**

This article cites 5 articles, 1 of which you can access for free at:
[http://jnnp.bmj.com/content/68/5/679.1#BIBL](http://jnnp.bmj.com/content/68/5/679.1#BIBL)

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
[http://group.bmj.com/group/rights-licensing/permissions](http://group.bmj.com/group/rights-licensing/permissions)

To order reprints go to:
[http://journals.bmj.com/cgi/reprintform](http://journals.bmj.com/cgi/reprintform)

To subscribe to BMJ go to:
[http://group.bmj.com/subscribe/](http://group.bmj.com/subscribe/)