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 suggesting 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 subjects 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 3.0.

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 subjects 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 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 the control of transcription factor 8 (TCP8), 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 provide 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 lod 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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**Table 1** Transmission disequilibrium testing results

<table>
<thead>
<tr>
<th>Marker</th>
<th>Hap</th>
<th>( \chi^2 )</th>
<th>( p ) Value</th>
<th>Primers</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL2</td>
<td>0.89</td>
<td>7.31</td>
<td>4.012</td>
<td>AAA GAG ACC TGG TAA CAC TGG TCT CCC TGG CCG CC</td>
</tr>
<tr>
<td>TCF8</td>
<td>0.73</td>
<td>0.08</td>
<td>2.096</td>
<td>AGA GGA TCC TGT TCA CTA CTG TGG GAA TTC TTA CTA CTG AGG</td>
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<tr>
<td>D14S1419</td>
<td>0.56</td>
<td>2.31</td>
<td>3.51</td>
<td>TAG GGA CAG CCA GTT CAT TA CAA TTA ATG TAA AAA TTA GCC A</td>
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<tr>
<td>D14S1420</td>
<td>0.67</td>
<td>0.74</td>
<td>2.69</td>
<td>TGT TTG AAG GGA GGA GTT GCC ACT CCA GTT CTA CTG TTT TTG</td>
</tr>
<tr>
<td>D14S826</td>
<td>0.74</td>
<td>1.74</td>
<td>4.78</td>
<td>TCT CTA AAG CTA CTA TAA CCC AG TGC TGT TGC ACT CAG GTA GCT A</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/GENTYPER 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.

**References**


We describe a patient with Alzheimer’s disease who developed coma a few days after starting low dose trazodone and ginkgo biloba.

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. Vitamin E was also discontinued and from March 1999 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 improved 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.
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 been explained 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 some clinical circumstances, adverse effects of similar magnitude as traditional drugs.

We hypothesise that, in our patient, on the one hand flavonoids provided a subclinical increase of the GABAergic activity through a direct effect on the BDZ receptor, whereas on the other increased CYP3A4 function and mCPP production, inducing a further enhancement of GABAergic activity that became clinically apparent. Flumazenil 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.

Bickerstaff’s brainstem encephalitis subsequent to Campylobacter jejuni enteritis

Bickerstaff's brainstem encephalitis (BBE) is characterised by acute ophthalmoplegia 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 Close speculated that the aetiology of BBE is similar to that of

2 Hamik A, Peroutka SJ. 1-(m-Chlorophenyl)piperazine (mCPP) interactions with neurotransmitter receptors in the human brain. Biol Psychiatry 1989;25:569–75.
Guillain–Barré syndrome (GBS) because arthralgia 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 its pathogenesis. A review of the literature in English turned up eight cases of BBE in which the pathogen 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 subsequent to Campylobacter jejuni enteritis.

A 17-year-old youth had fever and diarrhea that cleared up over a period of 5 days. Eight days after the resolution of this illness, he experienced unsteadiness (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, and there was mild weakness in the four limbs. Tendon jerks were brisk. Babinski’s sign was negative. Paraesthesiae of the glove and stocking type were present. The white blood count, C-reactive protein, and erythrocyte sedimentation rate were normal. Protein in CSF was 30 mg/dl with 7 cells/ul. The tentative diagnosis was brainstem encephalitis. Acyclovir was given intravenously for 5 days and antiviral treatment was discontinued for 3 days. Brain MRI showed no brain abnormality on days 5 and 12. On day 7, the patient became confused. Upward gaze and lateral gaze to the left were impossible, and downward and lateral gaze to the right were moderately impaired. Babinski’s phenomenon and oculocutaneous reflexes were absent. He developed palatal and lingual weakness. Muscular weakness was severe in the distal part of the arms and moderate in the legs. On day 9, motor and sensory nerve conduction velocities were normal, but an EEG showed bilateral diffuse theta and delta activity at rest. He was given 0.2 g/kg human immunoglobulin (Velenø, Tjeiin, Tokyo, Japan) daily for 5 days, starting on day 8. Consciousness disturbance (drowsiness and confusion), hyperreflexia, and tetraparesis as well as external ophthalmoplegia and ataxia of the cerebellar type. Serologic and isolation of the bacterium from his faeces confirmed prior C. jejuni infection. BBE was diagnosed because five (cases 6, 7, 8, 13, and 18) of the 18 patients with antecedent infection described by Al-Din et al. (Bickerstaff being one of the authors) had limb weakness. This diagnosis was supported by the presence of anti-GQ1b IgG antibody, a serological marker of BBE and Miller Fisher syndrome.4 Overlapping BBE and GBS was another possible diagnosis, and this has been reviewed elsewhere.6 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.7 The presence of that second case are 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 ataxic-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 CSF of this 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, GD1b, GT1b, or GQ1b epitopes. 8 Goodyear et al. immmunised 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.9 Infection by C. jejuni bearing a GT1a-like or GQ1b-like lipopolysaccharide may induce the production of anti-GT1a or anti-GQ1b IgG antibody, which then may bind to ocular motor nerves causing paresies 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 immunoglobulin (IVIg), should be used. Some patients with BBE have responded favourably to plasmapheresis,10 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.

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Myelopathy associated with Hashimoto’s disease

Encephalopathy associated with Hashimoto’s disease was first reported by Brain et al in 1966.11 Hashimoto’s encephalopathy is a steroid responsive relapsing disorder associated with Hashimoto’s disease that often presents with stroke-like episodes, ataxia, and cognitive impairment. Diagnostic testing usually shows a euthyroid state with increased thyroid autoantibodies, increased CSF protein, and EEG abnormalities. We present the first case of myelopathy associated with Hashimoto’s disease, followed 2 months later by encephalopathy.

A 70 year old housewife was admitted to our hospital on 28 July 1997. Her leg had felt heavy for a month, and she was unable to walk for several days before admission due to weakness in the left leg. She had been diagnosed with Hashimoto’s disease at the age of 57 and treated with thyroxin. On January 11 1998, she had developed dysphagia and weakness in the left arm and leg. Brain CT, radiography of the cervical spine, and CSF findings were normal at this time. She gradually recovered after this. On 31 January 1997, she was experiencing weakness in her left leg, which gradually disappeared over 2 months.

On physical examination, the blood pressure was 114/62 mm Hg. She had marked scoliosis. Neurological examination indicated a decrease of pain and temperature sensations on the right side and decrease of position and vibration sensations on the left side of the body below the Th7 level. Her muscle...
strength was evaluated as 2/5 (grade) in the left lower limb and 3/5 in the right lower limb by manual muscle test. Extensor plantar response was present on the left. Routine haematological and blood chemistry findings were within the normal range except for a mild increase of glutamic oxaloacetic transaminase (46 U/l, normal range 10 to 27), glutamic pyruvic transaminase (45 U/l, normal range 5 to 33) and r-globulin (34%, normal range 9.0 to 18.3). The serum free triiodothyronine (3.1 µg/ml) (normal range 2.4 to 4.5), free thyroxine, 1.2 ng/dl (normal range 0.8 to 1.7), and thyroid stimulating hormone (TSH) concentrations, 4.84 µU/l (normal range 0.5 to 5.0), were normal. The antithyroid globulin antibody titre was 1/409600 and the antithyroid microsomal antibody titre was 1/102400. Serological tests for syphilis and HTLV-I were negative. Vitamin B12, folate, angiotensin converting enzyme, ANA, anti-ds-DNA, ENA complex, and antiphospholipid antibody were normal or negative. Concentrations of circulating immune complexes were raised in blood (3.9 µg/ml, 0 to 2.9). The CSF was under normal pressure and contained 3 lymphocytes/µl, glucose 59 mg/dl, and mildly raised protein concentration at 50 mg/dl. Oligoclonal bands and myelin basic protein were absent. IgG index was normal. Further immunological results showed the titre of antithyroid microsomal antibodies in the CSF to be 1/128 and the titre of antithyroglobulin antibodies in the CSF to be 1/1600. A thoracic spinal MRI examination and myelography showed normal findings. She was given 500 mg intravenous methylprednisolone for 3 days. A few days later she made a marked improvement in muscle strength in her feet.

On 10 August 1997 she developed an abrupt onset of somnolence and disorientation. She was afibrile. Subsequently her respiration became irregular with short apnoic spells. Funduscopic examination was normal. She had spontaneous myoclonus in her right arm. Repeated CSF investigations showed a predominantly mononuclear pleocytosis (9 cells/µl) and raised protein concentration (74 mg/dl). An EEG showed diffuse slowing of background rhythm with sharp waves in several regions. Assuming a meningoencephalitis of possible viral origin, acyclovir was administered intravenously for 10 days. Polymerase chain reaction (PCR) studies showed herpes simplex virus and varicella zoster virus were negative. She was given 500 mg intravenous methylprednisolone for 3 days, then oral prednisolone. Her level of consciousness improved rapidly over the next several days. She was fully alert 7 days after initiation of steroid therapy. Steroid dosage was slowly tapered and maintained at 10 mg daily. She remained well for 18 months on steroid therapy. Cerebral MRI disclosed bilateral high signal areas in frontoparietal white matter on T2 weighted images. These findings were similar to those seen before her encephalopathy. Repeat spine MRI on 5 September 1997 showed previously unrecognised high intensity area by the T2 weighted image, on the left side of the cord at the level of the fifth and sixth thoracic vertebrae (figure). 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 concentration 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, sclerosis, and vascular accident, are known to cause myelopathy. The lack of typical findings of brain MRI and oligoclonal bands as well as myelin basic protein 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 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 postulated that a toxic effect of TRH on the CNS had an important role in Hashimoto’s encephalopathy.2 In our patients antithyroid antibodies were detectable not only in serum but also in CSF. Shaw et al 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 as well as in serum.


For those not versed in the history of this text, Douglas McAlpine, Nigel Compston, and Charles Lumsden, in 1955, authored its forerunner 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 Weinschenker. Finally, and perhaps for the clinician most imposingly, 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 disappointing 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 simulating 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".

IAN BONE


Advances and Technical Standards in Neurosurgery was created in 1974 as an adjunct 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 amyotrophic 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.
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