Matters arising

HLA typing and T-cell subpopulations in multiple sclerosis

Sir: Recently Hughes and co-workers have reported in this journal an association between the presence of HLA-DR2 and low CD8+ cells in multiple sclerosis patients and their cohabiting relatives. This finding was obtained from two partially different series of multiple sclerosis patients, relatives and unrelated healthy controls whose blood lymphocyte subpopulations were serially determined for several months. With a very similar protocol we have followed up 46 multiple sclerosis patients for 18 months and, in agreement with Hughes’ group and other investigators we found that chronic progressive multiple sclerosis patients have significantly less CD8+ lymphocytes or high CD4/CD8 ratios.

Now we have concluded the HLA typing of 38 out of 46 multiple sclerosis patients originally included in that study. Our results, which are summarized in the table, are at variance with the results obtained by Hughes from a lower number of patients. HLA-DR2 positive subjects do not differ from negative ones with respect to lymphocyte subset mean percentages.

DR2 is the most frequently found HLA phenotype in Caucasian multiple sclerosis patients. HLA-A3 and -B7 are also reported to be more represented in multiple sclerosis subjects than in the normal population. On the contrary HLA-B12 phenotype is negatively associated with the disease, almost in Italians. Consequently we correlated the presence or absence of these HLA phenotypes to lymphocyte subpopulation numbers. The results, similarly to what we found for HLA-DR2, were negative for a significant association (data not shown).

Our conclusion is that HLA-DR2 and reduced CD8+ cells are independently associated with multiple sclerosis.

Table

<table>
<thead>
<tr>
<th>CD3%</th>
<th>CD4%</th>
<th>CD8%</th>
<th>CD4/CD8</th>
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<tbody>
<tr>
<td>HLA DR2 + (n = 11)</td>
<td>74.2 ± 5.9</td>
<td>48.3 ± 8.9</td>
<td>30.4 ± 8.4</td>
</tr>
<tr>
<td>HLA DR2 - (n = 27)</td>
<td>74.6 ± 6.2</td>
<td>47.9 ± 7.1</td>
<td>30.3 ± 7.4</td>
</tr>
</tbody>
</table>

First, the percentage of HLA-DR2 positive patients is higher in DR2 + DR2 - compared to DR2 - DR2 +.

Second, the percentage of CD8+ lymphocytes is significantly less in DR2 + DR2 - compared to DR2 - DR2 +.

Third, the CD4/CD8 ratio is significantly higher in DR2 + DR2 - compared to DR2 - DR2 +.

We conclude that the association between HLA-DR2 and reduced CD8+ lymphocytes in multiple sclerosis is significant.

References


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Unexplained chronic subarachnoid bleeding and a slowly progressive neurological syndrome

Sir: Superficial haemosiderosis of the central nervous system has been postulated to be the explanation for the development of a slowly progressive clinical syndrome in a 9 year old child. The authors record supporting evidence including the presence of methemoglobin and haemosiderin-containing macrophages in the CSF. These findings together with reports of patients who have been documented to have a normal life, may lead to increased recognition of the clinical syndrome in patients presenting with the suggestive combination of anosmia, nerve deafness and long tract signs, as suggested in our own report of 2 such cases diagnosed at necropsy.

Dr Zwartz and colleagues note that the deposition of iron-containing pigment in the central nervous system results in gliosis and loss of neurons, but do not refer to the main pathological consequence of haemosiderosis, namely neuroaxonal

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Compston replies

Dr Zaccheroni and colleagues report that there is no difference in percentage of circulating CD8 cells in 11 HLA DR2 positive and 27 DR2 negative patients with multiple sclerosis. They comment that this finding contrasts with our demonstration of an association between HLA DR2 and periodic reductions in CD8 cells, irrespective of clinical status. There are important differences between the protocols used in these two studies which prevent comparison of the results. First, it is not clear whether the value quoted by the Italians for each lymphocyte subpopulation in DR2 positive and negative patients is a mean based on a single or serial observations in individuals. Secondly, our own observation related to the prevalence of periodic reductions in CD8 cells and not the absolute numerical value. Thirdly, we compared affected and unaffected individuals whereas Dr Zaccheroni and colleagues have restricted their analysis to patients with multiple sclerosis in all of whom low percentages of CD8 cells are to be expected (as they themselves point out) irrespective of HLA phenotype.
dystrophy. This is a metabolic response characterised by the appearance of so-called “spherooids”, ovoid axonal swellings believed to be a constant feature in superficial haemosiderosis. We have reported the finding of spheroids in the superficial layers of the cortex in three such cases as well as in the neighbourhood of haemosiderin deposits in eight cases of intracerebral haemorrhage. As spherooids were found in no other areas of these brains we suggested that haemosiderin results in NAD because of a local oxidative effect, perhaps due to lipid peroxidation.

This possibility may have therapeutic implications as it could perhaps lead to the use of antioxidants such as Vitamin E with hope of retarding clinical deterioration and in particular, dementia. In this connection it is of interest to note that neuroaxonal dystrophy is a feature of Vitamin E deficiency.

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References


Matters arising

Book reviews


This book traces the ideas that emerged in the early part of the 19th century that led to the development of the neurosciences as we know them today. This period was crucial to the development of science as a whole and in neuroscience the old anatomical and physiological concepts, some of them held for hundreds of years, were overthrown and replaced by the emerging disciplines of experimental science. The authors take as their theme the development of ideas in neuroscience in relation to the prevailing philosophical ideas of the time, and in relation to the available and emerging technologies that enabled the observations to be made that themselves led to recognition of the inadequacy of the earlier concepts. Thus the book is broken up into six main headings concerned with the cerebrospinal organisation of the nervous system, the nerve cell, reflex function, nerve function, brain function and the vegetating nervous system. The book is therefore concerned mainly with conceptual aspects of neuroscience, particularly derived from the concept of natural philosophy emerging from the work of the German philosophers in the early years of the 19th century, particularly Hegel and Kant and the development of the research tradition that occurred in universities such as Gottingen in the last years of the 18th century. These concepts were taken up in France and the United Kingdom, particularly in London and Edinburgh, and used as the basis for experimental observation. In the early part of this period of ferment, clinical observations, such as those on the effects of lesions in the nervous system, allowed the foundations of studies of the major motor and sensory pathways to be laid and led to the gradual formulation of ideas concerning localisation of cerebral function, and of the more difficult task of the localisation of intellectual function within the brain. The problem of localisation of function was particularly important in relation to the cultural context of the time. It had earlier been held, particularly by Haller, that the brain had functional equipotentiality. This was refuted by Gall who held that the brain was composed of several discrete parts each with its own peculiar properties each representing the specific intellectual and moral faculties. Much has been written elsewhere concerning this concept and the role of Flourens in substituting the concept of functionally distinct sub-divisions, concepts that led to current ideas on cortical localisation. The authors are particularly interesting in their account of the development of these ideas of brain function. The book is, throughout, thoroughly well researched and detailed in its account of the development of these concepts. References are given at the end of the book together with detailed accounts of individual contributions in relation to the references, and to individual scientists listed by name in alphabetical order. This is a splendid source of information on 19th century neuroscience.

For the amateur historian, however, the book lacks joie de vivre in that there is nothing said about the personal interactions between the scientists and the philosophers whose contributions are discussed in such detail. The casual reader would love to know the circumstances of the discussion between the proponents of Gall and Flourens, or the kind of reception received by Sir Charles Bell in his presentations and writings. Indeed, the contribution of localisation concepts of brain function in relation to the development of psychiatry receives somewhat scant attention. The ideas of the evolution of the nervous system arose out of some of these concepts and fall largely out of the scope of the book, although they receive adequate mention in the closing pages. One wonders how widely some of the ideas discussed were disseminated through 19th century culture and what was their influence on teaching, education, and the philosophy of everyday life. There is also much to be learned, and not really considered in this book, concerning the economics of research during this period. Many of the contributions of note appear to have been made by individual practitioners, perhaps working in relative isolation, and the institutionalisation of neuroscience, an important topic in relation to the dependence of scientific research on major funding from government sponsored institutions in the present time, receives no attention.

Altogether this is a splendid, if somewhat dry, account of the development of neuroscience concepts from the foundations laid in the Enlightenment by workers in the early part of the 19th century. An absolute must for anyone interested in history, neurology and neuroscience.

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Unexplained chronic subarachnoid bleeding and a slowly progressive neurological syndrome.
M Sadeh and J Braham

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