Multiple sclerosis and viruses

Evidence that human T-cell lymphotropic viruses are associated with multiple sclerosis may lead to identification of viruses that cause the disease — or to an addition to the list of failed candidates.

It is not every day that the Faroe Islands are mentioned in the scientific literature, but no contemporary review on the causes of multiple sclerosis is complete without a mention of them. While the disease was unknown in the Faroes before 1940, a mini-epidemic was recorded in the years after British troops were garrisoned there in 1940. There seems little doubt that an infectious agent was involved; it is now conventional to suppose that multiple sclerosis can be initiated by viral infection in genetically susceptible individuals. But which virus or viruses are the culprits?

Frustration has marked the hunt. By some counts, twelve separate viruses have at one time or another been implicated as initiators of multiple sclerosis. But in no case has the case been made to stick. So the first evidence of the frequent exposure of multiple sclerosis patients to a new virus type is bound to excite an equal mixture of interest and scepticism. Publication of the data, moreover, is bound to quicken the pace of the further research that will show whether the new type of virus is genuinely an initiator of multiple sclerosis, or whether it will join its dozen or so predecessors on a list of suspects. It is in this spirit that we publish, on page 154, the tantalizing but inconclusive evidence from Hilary Koprowski, Robert Gallo and their colleagues of an association between multiple sclerosis and the human T-cell lymphotropic viruses (HTLVs).

This provisional group of viruses comprises three members. HTLV-I was the first to be discovered, in 1980, and is the cause of adult T-cell leukaemia discovered in Japan. HTLV-II is a variant of HTLV-I; and HTLV-III (also known as lymphadenopathy-associated virus, LAV) is the cause of acquired immune deficiency syndrome (AIDS). Although HTLV-III lives up to this name in some ways, notably a propensity to infect human T lymphocytes, its nucleic acid sequence is not related to that of HTLV-I or HTLV-II. Another view, now strengthening, is that HTLV-III is more related to the lentiviruses than to the other HTLVs. Evidence comes from both structural comparisons and the fact that the HTLV-III can be found in brain tissues of certain AIDS patients (Shaw, G.M. *et al.* *Science* **227**, 117; 1985). Lentiviruses are animal viruses that cause progressive demyelinating diseases of the brain and spinal cord. Indeed, the disease caused in sheep by visna virus, the most studied of the lentiviruses, is often

said to be the best naturally occurring model for multiple sclerosis.

Inevitably, therefore, attention has been turned to the possibility that HTLV-III or a related virus is the cause of multiple sclerosis. Ironically, the evidence of Koprowski *et al.* is if anything more suggestive of an association between multiple sclerosis and HTLV-I or HTLV-II than with HTLV-III. Indeed there is no uniform response among the patients studied to tests for any of the three HTLV types; the authors say this conceivably indicates the presence of one or more entirely new HTLV-like viruses, possibly including a virus that combines some of the features of all three known HTLVs.

Leaving aside the identity of the viruses responsible for the signals detected in the tests, what and how strong are the signals, and to what extent can they be interpreted as evidence that the viruses in any way cause the disease? The signals are of two distinct types: the presence in the blood and cerebrospinal fluid of antibodies that cross-react with HTLV proteins, and the presence in cells cultured from cerebrospinal fluid of HTLV RNA. The former indicates that the viruses have been present, the latter that they are still present and active.

There are three problems in interpreting the antibody data. First, although it is clearly shown that the concentration of antibodies that cross-react with some HTLV proteins is greater in most serum and cerebrospinal fluid samples from multiple sclerosis patients than in various controls, such antibodies are not invariably present. Second, no consistent picture emerges as to which HTLV the antibodies are most closely related, although HTLV-I is much more frequently and usually more strongly implicated than HTLV-III. Third, and most important, it is already known that elevated concentrations of antibodies to measles and Epstein-Barr virus are frequently found in the cerebrospinal fluid of multiple sclerosis patients, throwing doubt on the significance of raised antibodies to other viruses.

For the data that indicate the presence of RNA that is related to HTLV RNA in cultured cerebrospinal fluid cells, at least there is no consistency of HTLV type. In the 4 out of 8 cases where RNA has been detected, it is related, though not very closely, to RNA of HTLV-I but not HTLV-III. When present, the RNA is detected in less than one cell in ten thousand,

which may at first seem too low to be of significance, but this rate is similar to the frequency of HTLV-III RNA in T cells of AIDS patients. Moreover, it is a general observation in chronic virus infections, including visna and measles, that only 0.1 to 1.0 per cent of cells in any tissue contain viral genetic information. Much more of a problem is that the controls are so far limited to two healthy subjects, neither of whom had HTLV-related RNA in the cells of their cerebrospinal fluid.

When Ashley Haase and his colleagues first reported measles virus RNA in several multiple sclerosis brains (*Science* **212**, 672; 1981), the data, together with those on elevated antibodies to measles virus in multiple sclerosis, made the measles virus a strong candidate as the initiator of the disease. But further investigations revealed that measles virus RNA can be detected almost as frequently in the brains of patients with other neurological and non-neurological diseases as in those with multiple sclerosis, weakening the case for the involvement of measles virus in multiple sclerosis, though not excluding it.

Clearly, more data, and particularly more controls, will be needed before the case for an HTLV-type virus as the initiator of multiple sclerosis can be realistically assessed: the National Multiple Sclerosis Society in New York has already organized several laboratories to begin participating in studies of the putative association with HTLV. There will also be intense efforts to try and isolate the virus or viruses that are the source of the HTLV-I-like RNA. Until that can be achieved, there can be little progress in understanding the variability of the HTLV-related antibodies in multiple sclerosis.

Even if a virus can be proved to be implicated in multiple sclerosis, it is likely to be merely the initiator of a chain of immunological events leading to demyelination of nerve fibres rather than a direct cause. It seems probable that the initial viral infection somehow triggers an autoimmune reaction against components of the myelin sheath of nerves. "The baroque complexities of contemporary immunology in its application to multiple sclerosis", as Byron Waksman puts it in summarizing current research on page 104, will require considerable unravelling before it is clear how the disease progresses from the triggering event.

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