

## Immunohistopathology to guide multiple sclerosis treatment

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Immunologists have often been accused of overly complicating medicine with details of molecules, cellular differentiation patterns, and insights with disputable usefulness. By contrast, the recognition that one subtle fact of medical history or clinical sign is the key to distinguishing between diagnoses, often with the implication of a completely different therapy, is a cornerstone of good medical practice. In today's *Lancet*, Mark Keegan and colleagues<sup>1</sup> show that immunopathological differentiation might lead to better therapies for complex disorders, such as multiple sclerosis.

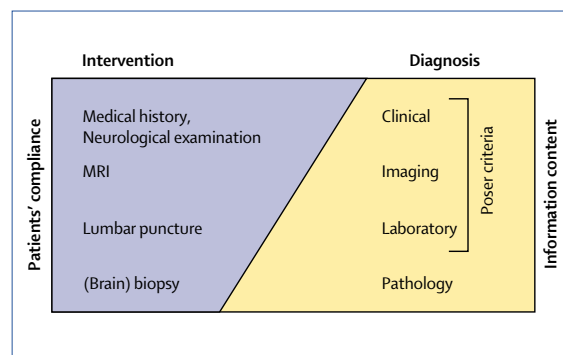
Multiple sclerosis is a multifactorial disease, with interactions between genetic and environmental factors via the immune system. MHC molecules, which present foreign antigens and self-antigens to T lymphocytes, are encoded by the highly polymorphic locus of the human leucocyte antigen on chromosome 6. Specific haplotypes of this susceptibility locus, in interaction with other genetic factors and environmental influences, might contribute to the various phenotypes of the neurological deficits (eg, relapsing-remitting versus primary-progressive, severity, course). Although no factor has been proven as the cause of multiple sclerosis, the pathological changes involve inflammatory processes that lead to the production of cytokines, chemokines, gelatinase-B/matrix-metalloproteinase-9, autoantibody-producing B lymphocytes, and autopeptide-recognising T cells, hence its classification as an autoimmune disease.<sup>2-5</sup> Current therapies for multiple sclerosis are disease-modifying, rather than real cures, and have been given to rather broad groups of patients with multiple sclerosis and solely on the basis of a clinical diagnosis. The cytokine interferon  $\beta$ , and the co-polymer glatiramer acetate, delay progression, but are both fraught with side-effects and high costs.<sup>6,7</sup> These elements constitute enough grounds to search for better, more efficient, and less expensive therapies. One way to achieve such therapies is to detail the subtle diagnostic differences, subcategorise patients who might respond better to a particular therapy, and assess the benefits.

Combinations of attacks, clinical evidence and para-clinical signs, including neuroimaging, evoked potentials, and laboratory findings of oligoclonal bands in the spinal fluid, or intrathecal immunoglobulin production,

are used in the classical Poser criteria for diagnosis of multiple sclerosis.<sup>8</sup> The IgG index—ie, the ratio of spinal fluid immunoglobulin to serum levels—is a marker that suggests the involvement of B lymphocytes and antibodies. The index correlates with the ratio of gelatinase B to A, a marker of innate immunity.<sup>9</sup>

The study by Keegan and colleagues is based on the combination of two studies: the clinical finding that total plasma-exchange might help in demyelination diseases,<sup>10</sup> and the refinement of the differential diagnosis of multiple sclerosis on the basis of careful histopathology of brain sections.<sup>11</sup> Similar to other frequent autoimmune diseases, such as rheumatoid arthritis and diabetes, multiple sclerosis is not just one disease. Instead, it forms a heterogeneous group of clinical and histopathological entities. For instance, T lymphocytes predominate in some forms of multiple sclerosis, whereas antibodies seem to be the culprit in other forms. Antibody formation against myelin antigens seems to precipitate a severe complement-mediated attack with a fulminant course.

The hypothesis to advance the therapy for multiple sclerosis was well formulated and tested by Keegan and colleagues. In retrospect, one might conclude that, if patients are discriminated on the basis of histopatho-



**Figure: Compliance versus information content in diagnosis of multiple sclerosis**

Various medical activities lead to diagnosis of multiple sclerosis. Recording medical history, neurological examination, and imaging are compliant methods for patients, doctors, and paramedics. Lumbar puncture and (brain) biopsy are more invasive. However, decrease in compliance (blue) is counterbalanced by increase in valuable information (yellow). Poser criteria, which contain and integrate clinical, imaging, and laboratory information, might be complemented with immunohistopathology analysis of brain biopsy to select carefully patients with multiple sclerosis, who might benefit most from total plasma-exchange therapy. Justified medical interventions thus lead to subtle differential diagnoses of histopathologically different forms of multiple sclerosis with implications for therapy.

logical analysis and if immunoglobulin deposition and complement activation are observed, possibly as a pathogenic factor, the elimination of damaging inflammatory factors should help and improve the neurological deficit. The conditions are, however, very strict and therefore the adherence to a good diagnostic protocol and selection of patients is important. Unfortunately, a brain biopsy was used. By comparison with other current diagnostic measures, biopsies decrease the compliance for patients considerably, therefore surrogate markers are needed (figure).

We do not know how total plasma-exchange works. The technique might eliminate pathogenic molecules or induce and restore beneficial humoral factors. This issue might be addressed in future studies by prospectively investigating, for example, complement-factor consumption, alterations of immunoglobulins, acute-phase reactants, cytokines, and balances between matrix metalloproteinases and inhibitors. In addition, the collection of individual plasma exchanges after informed consent might constitute an ideal opportunity to discover the elusive humoral pathogenic factor(s). By the study of autoantigens and antibodies in single patients, so-called nagged antibodies<sup>12</sup> or novel antigens might be discovered.

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## Vegetables, fruit, and cancer

A role for plant foods in the maintenance of health has been known for several thousand years. Plants and plant extracts also provide the bulk of the pharmacopoeia. In 1991, Steinmetz and Potter<sup>1,2</sup> summarised the available (largely case-control) data on cancer, vegetables, and fruit, concluding that the evidence was consistent with higher consumption being associated with a lower risk of many epithelial cancers. The 1997 World Cancer Research Fund report,<sup>3</sup> reviewing the available literature to the end of 1996, concluded that vegetables and fruit were probably or convincingly associated with a lower risk of cancers of mouth, oesophagus, lung, stomach, colorectum (vegetables only), larynx, pancreas, breast, and bladder. In October 2004, Hsin-Chia Hung and colleagues,<sup>4</sup> using data from the Harvard Nurses Health and Health Professionals follow-up studies,<sup>5</sup> concluded that vegetables and fruit were associated with a lower risk

of cardiovascular disease, but that the relation with cancer, overall, was null. Clearly there is an inconsistency here. Is there an explanation?

First, is Hung and colleagues' report<sup>4</sup> consistent with earlier findings from the Harvard investigators? Previously, Walter Willett's group at Harvard had reported lower risks in association with high intakes of vegetables and fruit for premenopausal, but not postmenopausal, breast cancer (and, in 1993, a reduced risk for all breast cancer with vegetables alone<sup>6</sup>), female lung cancer,<sup>7</sup> male bladder cancer but only for cruciferae,<sup>8</sup> non-Hodgkin lymphoma,<sup>9</sup> and prostate cancer (for fruit only).<sup>10</sup> Only for colon cancer have they previously reported no association with vegetables and fruit.<sup>11</sup>

In other cohort studies of breast cancer, high intake of vegetables and fruit was not associated with risk in the Leisure World Study<sup>12</sup> but showed reduced risk in the